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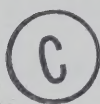
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THE PREPARATION AND SOME PROPERTIES
OF NEW PSYCHOTOMIMETIC AGENTS

BY



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A THESIS

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ABSTRACT

The primary objective of the research described in this thesis was the study of the syntheses and properties of compounds which might provide a further understanding of the structural features phenethylamines require to possess psychotomimetic activity. The types of compounds synthesized were methoxylated phenethylamines and their cyclic analogs, aminoindanes.

A preliminary pharmacological study of some selected examples of these compounds was undertaken. They were administered to rats and their gross pharmacological effects were compared with those caused by the potent hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)isopropylamine (DOM).

Previous studies showed that 1-(2,4,5-substituted phenyl)isopropylamines were extremely potent psychoactive agents. Since only four such compounds have been reported in the literature, further examples of compounds with this ring substitution pattern were synthesized. Of the six 1-(2,5-dimethoxy-4-substituted phenyl)isopropylamines prepared, four caused gross pharmacological effects in the rat similar to those observed with DOM. A similar effect was observed with an analog of DOM, namely N-(2,5-dimethoxy-4-methylphenethyl)hydroxylamine.

Four 2,4,5-trisubstituted phenylalanines were prepared and two were pharmacologically evaluated. Neither

appeared to induce effects in common with those produced by DOM.

Six compounds which were considered possible metabolites of DOM were synthesized before a study of the metabolism of DOM appeared in the literature.

The potent 'street drug' STP has been found to contain DOM. Some original reports in the literature describe STP as being much more potent than that observed with a pure sample of DOM. To determine whether the claimed exaggerated effects could have been the result of a by-product produced in the synthesis of DOM, a study of possible active side products was undertaken. Under the conditions employed, in addition to DOM, 2,5-dimethoxy-4-methylphenylacetone, the oxime of 2,5-dimethoxy-4-methylphenethyl)hydroxylamine, 2,5-dimethoxy-4-methylbenzonitrile, and 2,5-dimethoxy-4-methylbenzylamine were isolated. The latter compound is toxicologically interesting since it closely resembles a compound which has been reported to cause uterine contractions in very low doses. Similarly, 3,4-methylenedioxybenzylamine was recovered in an attempted synthesis of 3,4-methylenedioxyamphetamine (MDA).

Examination of two different street samples of DOM (STP) failed to show the presence of any of the above-mentioned compounds. The study, however, showed that each sample, in addition to DOM, possessed other basic components, none of which were identified.

Two oximes investigated in the study, i.e. 2,5-dimethoxy-4-methylphenylacetone oxime and 2,5-dimethoxyphenylacetone oxime, underwent an unusual fragmentation on electron impact. This process involved the expulsion of a methoxyl group with concurrent formation of a cyclic nitronium ion. To determine whether this ortho-effect was of any value in characterizing methoxylated amphetamines or their metabolites, the mass spectra of three such compounds were recorded and interpreted.

An investigation of the positional requirements of the nitrogen atom of phenethylamine psychotomimetic drugs was next undertaken. This study involved the synthesis of compounds in which the nitrogen atom was held in a rigid conformation. The first compound prepared was the cyclic analog of DOM, namely 2-amino-4,7-dimethoxy-5-methylindane. A preliminary pharmacological evaluation revealed that this compound caused some effects in rats similar to those caused by DOM. Therefore, several derivatives of this structure were prepared. These included the 1-ethoxy, 1-propoxy, and 1-chloro analogs as well as the 2-dimethylamino-4,7-dimethoxy-6-methyl-1-indanols, 2-dimethylamino-4,7-dimethoxy-5-methylindane, and 2-(dimethylamino)methyl-4,7-dimethoxy-5-methylindane.

Because of the positive psychopharmacological activity of 2-amino-4,7-dimethoxy-5-methylindane, additional 2-amino-4,7-dimethoxy-5-substituted indanes were synthesized.

Although attempts to prepare these compounds by a general procedure were unsuccessful, two derivatives were obtained. These were the 6-unsubstituted and 6-bromo derivatives. The latter compound, when tested in a rat, appeared to possess psychoactive properties, as did 2-amino-5-methoxyindane which was also prepared.

Of the five 1-aminoindane derivatives studied, only one, (1-amino-4,7-dimethoxy-6-methylindane), was tested in rats; it failed to induce DOM-like effects.

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INTRODUCTION

The use of mind altering drugs can be traced as far back as man himself. Despite varied geographical locations, few societies have failed to use some form of these compounds. Lewin⁽¹⁾ wrote:

"The passionate desire which...leads man to flee from the monotony of everyday life... has made him instinctively discover strange substances. He has done so, even where nature has been most niggardly in producing them and where the products seem far from possessing the properties which would enable him to satisfy this desire."

The predominant use of these drugs has been to achieve a mystical experience, a bridge with the gods. Those under the influence of these drugs were believed to have supernatural powers of healing and divination. In addition, these drugs were employed as medicinals and as agents to increase sociability, much like alcohol in present-day Western society. Some 60 species of plants are employed as intoxicants, the most important being coca, tobacco, opium, poppy, and cannabis.

The first and most potent psychoactive drug of non-plant origin, LSD-25, was discovered in 1943 by Albert Hofmann^(1a). The transient pharmacological effects of this drug closely resembled some aspects of psychosis. This similarity gave great impetus to studies attempting to relate the deep secrets of mental illness to a chemical process. Subsequently, great advances were, and still are being made in the areas of neurochemistry, neuropharmacology, and neurobiology.

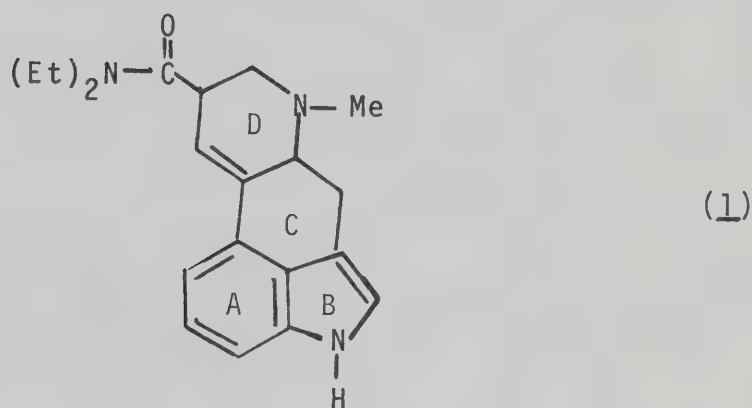
The known hallucinogens fall into two broad groups:

(a) those containing nitrogen, most of which are alkaloids or related compounds, and

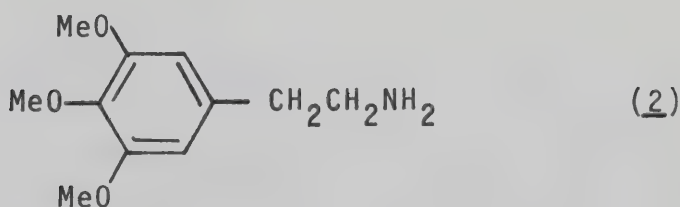
(b) those devoid of nitrogen.

The hallucinogens are, however, more conveniently classed into seven separate groups ⁽²⁾:

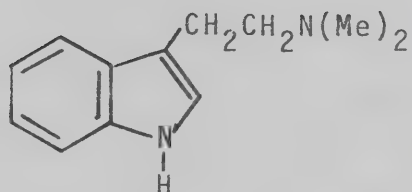
1. lysergic acid derivatives, LSD or LSD-25 (1) being the prototype;



2. phenylethylamine derivatives, 3,4,5-trimethoxyphenethylamine (mescaline) (2) being the prototype;

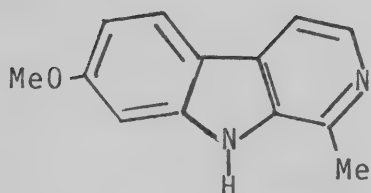


3. indolealkylamines such as dimethyltryptamine (3);



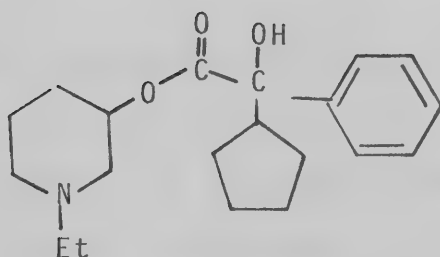
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4. other indole derivatives such as harmine alkaloids (4);



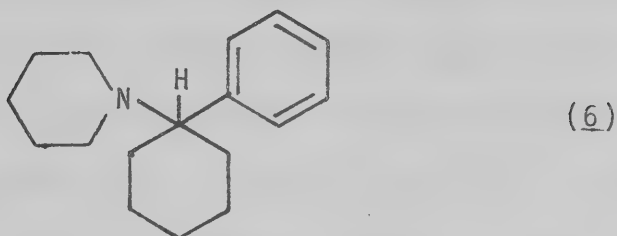
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5. piperidyl benzilate esters such as N-ethyl-3-piperidyl cyclopentyl phenyl glycolate (JB-329 Ditran) (5);

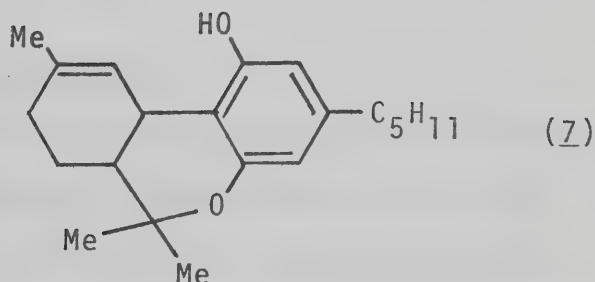


(5)

6. 1-phenylcyclohexyl compounds such as phenylcyclidine (Sernyl[®]) (6) and



7. a miscellaneous group of varying chemical structures such as Δ' -tetrahydrocannabinol (Δ' -T.H.C.) (7) or Kowain.



The structure-activity relationships of psychotomimetic drugs are difficult to study since there are no simple chemical or in vitro systems available for their pharmacological evaluation. In vivo studies may not always reflect the true potencies at receptor sites. Enhanced resistance to metabolic degradation or increased capacity

to pass the blood-brain barrier are important factors to be considered. Even after penetration into the brain, drug activity may be determined by regional cellular or sub-cellular variations. In spite of these limitations, studies on psychotomimetic drugs are performed and suggest that differences in activity do not appear to be attributable simply to these above-mentioned factors, and that it might be possible to deduce which structural elements are most essential for psychotomimetic activity.

A brief historical review of some of the more commonly used mind altering substances is now presented. That which follows is a summary of a more expanded article by Hollister⁽²⁾ on this subject.

Lysergic Acid Diethylamide (LSD)

In the course of preparing analogs of a natural ergot alkaloid, Stoll and Hoffman synthesized LSD in 1938. However, it was not until 1943 that its psychotomimetic properties were discovered when it was accidentally ingested by Hoffman. Lysergic acid is the chemical basis from which LSD is synthesized. It is also the basic structure for the natural ergot alkaloids, which are products of a fungus which grows on grains, especially rye. LSD is the most potent of all known hallucinogens and is active after oral ingestion of doses as low as 20 to 30 μ g. Although many modifications of LSD have been reported, none of the

derivatives are as active as the parent. Because the effects of the drug closely resemble a model psychosis, numerous investigations involving LSD have been undertaken. In the past decade LSD has gained popularity as 'a mind expanding drug' and a hallucinogen in most western societies.

Peyote (Mescaline)

Peyote, a cactus which grows in Northern Mexico, has been employed for religious and magical purposes. Upon ingestion of the plant, vivid hallucinations involving intense colors and geometric patterns are said to occur. Initially used only by Mexican Indians, the use of peyote spread to the North American Indians and by the 1880's a fully developed peyote religion had unfolded. It then spread rapidly over North America to become the most widespread American Indian drug religion. The peyote cult still remains active in the Southwestern United States.

The hallucinogenic constituent of peyote, mescaline, was first isolated in 1896 and characterized in 1918.

Mexican Mushrooms (Psilocybin)

The cult of the divine mushroom in Central America can be traced back as far as 1500 B.C. and its use probably extended from the Aztecs in Mexico to the Mayas in Guatemala. The use of these intoxicants was generally associated with religious ceremonies.

These mushrooms (genus Psilocybe) were found to

contain two equally active psychotomimetic agents, psilocybin and psilocin.

Ololiuqui

Ololiuqui is an Aztec name for the hallucinogenic seeds of several species of plants found in Mexico. The seeds contain a mixture of alkaloids of lysergic acid and its derivatives. The hallucinogenic activity has been attributed to d-lysergic acid amide (ergine), d-isolysergic acid amide (isoergine), elymoclavine, and lysergol. Like the sacred mushrooms and peyote, the use of ololiuqui was mainly associated with religious functions. Osmund, after taking the seeds, described their effect as causing a state of apathy and indifference accompanied by increased visual sensitivity.

Hashish (Cannabis)

The term hasheesh is Arabic and literally means dried herb. Hashish is the resin located in the flowering clusters and the top leaves of the female hemp plant. The resin is ingested as an additive to a drink, as a candy, or it is eaten directly. The dried tops and flower pistils are often powdered, then smoked in cigarettes. Its use in India and China has been mentioned by Herodotus, a Greek historian (484 - 424 B.C.). In the eleventh century it was used by a religious-political sect who became known as assassins from the Arabic word hashishin (hemp-eaters).

This sect adopted murder or assassination as a religious duty. Recently the use of hashish in Western society has become very popular. Although its pharmacology has not been investigated extensively, its widespread use has recently stimulated such studies.

Belladonna Alkaloids and Other Anticholinergics

The alkaloids, atropine, hyoscyamine, and scopolamine, which are found in several plant species, have been used to cause hallucinations and states of delirium. The Greeks used these drugs to evoke prophecies. In the middle ages sorcerers used these compounds in potions to conjure up demons. Datura stramonium has been smoked to induce a state of intoxication by various African and Middle East tribes. American Indians also used Datura, mainly in religious ceremonies and as inebriants during painful initiation ceremonies. Recently, a large number of anticholinergics, including the potent piperidyl benzilate esters, have been synthesized. These compounds also produce a state of profound delirium which can last for several days.

Bufotenin and Related Compounds

Bufotenin, first discovered in the skin glands of toads (Bufo vulgaris), from which the name is derived, has also been found to be present in the leaves and seeds of certain South American plants. Some Indian tribes used this intoxicant as a snuff called cohoba. The snuff was thought

to render the warriors fearless and insensitive to pain. The chemically closely-related compound, N,N-dimethyltryptamine, is also found in plants of the same region and has been used in an intoxicating drink. Both bufotenin and N,N-dimethyltryptamine are only slightly effective when taken orally as compared with intravenous dosage. Both these materials have been used as hallucinogenic agents to a limited extent in North America.

Harmala Alkaloids

A narcotic drink made from plants of the family Malpighiaceae has been used by Western Amazonians. The active principles were found to be harmine and similar alkaloids. The drink was used in religious ceremonies and on festive occasions.

Ibogaine

Ibogaine is an alkaloid derived from the root bark of Tabernanthe iboga which grows in the French Congo. This hallucinogenic compound was associated mainly with religious functions.

Kat (Catha Edulis)

Kat is an alkaloid found in the twigs and leaves of the tree Catha edulis and was used by Ethiopians, Abyssinians, Yemenese, Adenese, Kenyans, Somalilandese, and South Africans. This material is ingested by a variety of methods and is usually taken at social gatherings for its euphoriant

effect. In large doses it causes an agitated psychosis and hallucinations. A large amount of the drug is currently consumed in Africa and the Middle East.

Kava

Kava is an intoxicating drink widely used throughout the South Pacific. It is prepared from the root of the indigenous plant, Piper methysticum, and is used in social and religious settings. Its effects are initially euphoriant, followed by sedation. Some habituation to Kava has been noted.

Soma

Soma is an intoxicating drink prepared from a number of plants. It has been used ritually by the Aryans and the Indo-Iranians. The drink was believed to give courage, health, long life, and immortality to the drinker's soul.

Methoxylated Phenethylamines

Recently a large number of methoxylated phenethylamines have been synthesized, many of which were found to possess psychotomimetic properties. This class of compounds is the major topic of the present thesis, and hence will be discussed in detail in the next section.

LITERATURE SURVEY

The present study involves the synthesis and preliminary pharmacology of some potential psychotomimetic drugs. These compounds are derivatives of two general chemical classes, namely phenethylamines and aminoindanes. Hence, this study will be discussed under these two main headings.

A major portion of this study involves the synthesis of α -methylphenethylamines, phenethylamines, and α -carboxyphenethylamines (phenylalanines). Therefore a summary of the pertinent structure-activity relationship studies of psychotomimetic phenethylamines as well as methods employed in their synthesis will be presented in this section. Also presented is a review of studies involving the preparation of amino acids designed as psychotomimetic agents.

The synthesis of possible metabolites of a methoxylated phenethylamine, 1-(2,5-dimethoxy-4-methylphenyl)-isopropylamine, was also investigated in this study. Hence a summary of some metabolic studies of related compounds is discussed.

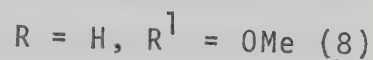
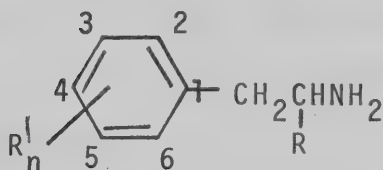
The second major portion of this study involves the synthesis of aminoindanes. Although these compounds are not known to be psychotomimetic, many derivatives of 1- and 2-aminoindanes possess a variety of psychoactive properties. These properties as well as some pertinent chemistry is discussed.

I. PSYCHOTOMIMETIC PHENETHYLAMINES AND RELATED COMPOUNDS

Structure-Activity Relationship Studies of Psychotomimetic Phenethylamines

Although mescaline has a long history, compounds chemically related to this psychotomimetic agent have only recently been prepared and investigated. This class of hallucinogens encompasses a great variety of structural analogs which possess varying degrees of activity. This has led to the postulation of several theories which are intended to explain the psychotomimetic activity of these compounds.

Since a major portion of the present study is either directly or indirectly related to this class of hallucinogens, a review of the important aspects pertinent to the study will now be presented.



The first class of compound to be discussed is the methoxylated phenethylamines (8). Smythies et al. (3,4) studied the relationship between psychotomimetic activity

and the position of the methoxy substituent on the benzene ring. They found that all of the monomethoxylated isomers were inactive in doses of 25 mg/kg. Shulgin⁽⁵⁾ however, reported that 4-methoxyphenethylamine was almost as potent as mescaline. All of the dimethoxylated phenethylamine isomers, when evaluated by the Sidman avoidance response technique, were found to be inactive, although 3,4-dimethoxyphenethylamine had previously been reported to possess activity in rodents⁽⁶⁻⁹⁾. Mescaline was the only trimethoxylated isomer which was found to possess activity. Shulgin⁽⁵⁾ reported that 2,4,5-trimethoxyphenethylamine was as potent a compound as mescaline. Of the tetra-substituted derivatives, 2,3,4,5-tetramethoxyphenethylamine (approximately 2 mescaline units*) was the only isomer possessing activity. 2,3,4,5,6-Pentamethoxyphenethylamine was found to be seven times as potent as mescaline. Several methylenedioxyphenethylamine analogs were prepared and the following potencies reported⁽⁵⁾: 3,4-methylenedioxyphenethylamine, 0.2 M.U.; 3-methoxy-4,5-methylenedioxyphenethylamine, 1.0 M.U.; and 2-methoxy-3,4-methylenedioxyphenethylamine, 5.0 M.U.

The α -methylphenethylamines (phenylisopropylamines

* Potency of a psychedelic drug is the minimally detectable dose in humans or ED₅₀ in animals and is expressed as mescaline units (M.U.), defined as the effective dose of mescaline divided by the effective dose of the compound evaluated.

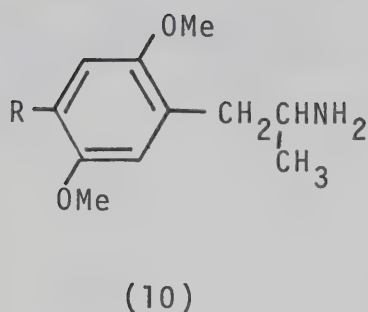
Table I
Structure-Activity Relationships
of Methoxylated Phenylisopropylamines (9)

Substitution Pattern					Activity, Mescaline Units
2	3	4	5	6	
H	H	OCH ₃	H	H	5
OCH ₃	OCH ₃	H	H	H	-
OCH ₃	H	OCH ₃	H	H	5
OCH ₃	H	H	OCH ₃	H	8
OCH ₃	H	H	H	OCH ₃	-
H	OCH ₃	OCH ₃	H	H	1
H	OCH ₃	H	OCH ₃	H	-
H	OCH ₃	OCH ₃	OCH ₃	H	2.2
OCH ₃	H	OCH ₃	OCH ₃	H	17
OCH ₃	OCH ₃	OCH ₃	H	H	2
OCH ₃	OCH ₃	H	OCH ₃	H	4
OCH ₃	OCH ₃	H	H	OCH ₃	13
OCH ₃	H	OCH ₃	H	OCH ₃	10
O	-CH ₂ -O	H	H	H	-
H	O	-CH ₂ -O	H	H	3
H	OCH ₃	O	-CH ₂ -O	H	2.7
OCH ₃	H	O	-CH ₂ -O	H	12
OCH ₃	O	-CH ₂ -O	H	H	10
O	-CH ₂ -O	OCH ₃	H	H	3
O	-CH ₂ -O	H	OCH ₃	H	-
O	-CH ₂ -O	H	H	OCH ₃	-
OCH ₃	O	-CH ₂ -O	OCH ₃	H	12
OCH ₃	OCH ₃	O	O	H	5
H	OCH ₃	O	-(CH ₂) ₂ -O	H	1
OCH ₃	OCH ₃	OCH ₃	OCH ₃	H	6
OCH ₃	OCH ₃	OCH ₃	H	OCH ₃	-
OCH ₃	OCH ₃	H	OCH ₃	OCH ₃	-
OCH ₃	OCH ₃	OCH ₃	OCH ₃	OCH ₃	-
OC ₂ H ₅	H	OCH ₃	OCH ₃	H	7
OCH ₃	H	OC ₂ H ₅	OCH ₃	H	15
OCH ₃	H	OCH ₃	OC ₂ H ₅	H	7
OC ₂ H ₅	H	OC ₂ H ₅	OCH ₃	H	-
OC ₂ H ₅	H	OCH ₃	OC ₂ H ₅	H	-
OCH ₃	H	OC ₂ H ₅	OC ₂ H ₅	H	-
OC ₂ H ₅	H	OC ₂ H ₅	OC ₂ H ₅	H	-
OCH ₃	H	CH ₃	OCH ₃	H	80

or amphetamines) (9) were shown to be more active than the corresponding analogs of the previous group; therefore the former series has been more extensively studied than the latter. It is thought⁽¹⁰⁾ that increasing the side chain of the phenethylamine to 3-carbons, thereby forming phenylisopropylamines, makes the amino group less amenable to deamination by enzymatic attack. However, extension of the side chain beyond the optimum 3-carbon chain length results in a decrease of activity⁽¹⁰⁾.

Most of the analogs of the methoxylated phenylisopropylamines have been prepared and are summarized⁽⁵⁾ in Table I. It is evident from this table that maximum activity is obtained when the 4-position is substituted. Incorporation of a methoxy group into an ortho-position usually enhances activity. With a few exceptions meta-methoxylation results in a decrease in activity, while conversion of two adjacent methoxy groups into a methylenedioxy group generally increases activity.

Several compounds have been reported which differ only in the nature of the substituent at the 4-position while retaining the 2,5-dimethoxy substitution pattern. The 4-methoxy analog (10a) was the most potent isomer of the trimethoxyphenylisopropylamines⁽¹¹⁾. 2,5-Dimethoxy-4-ethoxyphenylisopropylamine (10b) is also reported to be relatively active⁽¹²⁾. The 4-methyl analog (DOM) (10c) and the 4-ethyl analog (DOEt) (10d) are the most potent of



R = OMe (10a)

R = OEt (10b)

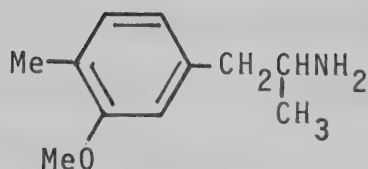
R = Me (10c)

R = Et (10d)

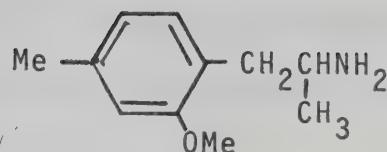
R = Br (10e)

the known psychotomimetic phenethylamines⁽⁵⁾. DOEt is approximately twice as potent as DOM. Studies in humans^(13,14) however, showed that DOEt was not a psychotomimetic agent but rather was a psychic energizer. Another example of this substitution pattern, 1-(4-bromo-2,5-dimethoxyphenyl)-isopropylamine (10e), has recently been prepared and evaluated^(15,16). It was found to induce a mescaline-like action more profound than an equal amount of DOM. In the latter study five other bromo-isomers were described. These were found to be either less active than (10e) or inactive.

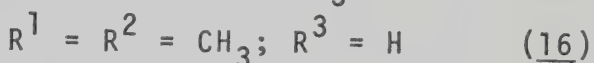
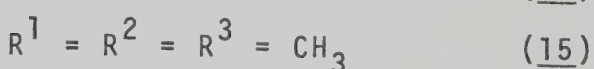
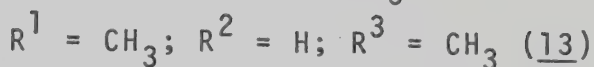
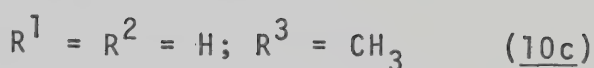
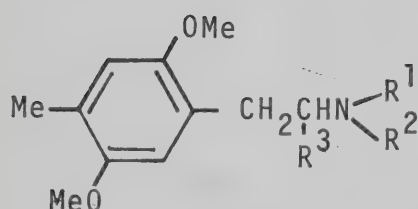
Because of the relatively high potency of DOM as compared with other methoxylated phenethylamines, several structural modifications of DOM were investigated by Ho et al.⁽¹⁷⁾. They found that 1-(3-methoxy-4-methylphenyl)-isopropylamine (11) was as active as DOM in disrupting behaviour in mice and had a longer duration of activity. In contrast, 1-(2-methoxy-4-methylphenyl)isopropylamine (12) was found to be inactive.



(11)

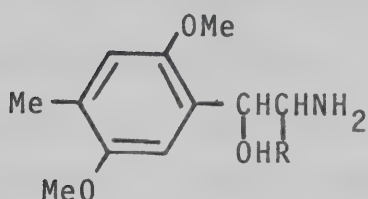


(12)



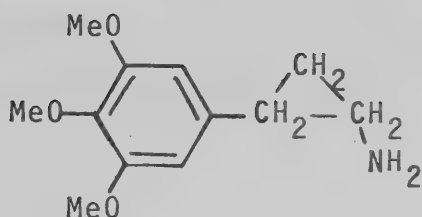
Ho et al.⁽¹⁸⁾ further modified DOM (10c) as shown by structures (13 - 16). Compounds (10c) and (14) were the most active in disrupting rat behaviour. Compound (14) was three-fourths as active as (10c). N-Methylation of both the phenylisopropylamine and phenethylamine series resulted in a 5- and 7.5-fold decrease in activity. No additional decrease in activity was detected in the dimethyl derivative (16). Unlike DOM, which is known⁽¹⁸⁾ to decrease phenobarbital-induced sleeping time, compounds (13) and (16) had no effect on phenobarbital-induced sleeping time in mice.

In another publication⁽¹⁹⁾ Ho et al. reported on the preparation of compounds (17) and (18), but did not describe any pharmacology.



R = H (17)

R = Me (18)



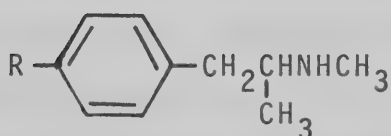
(19)

Pinder et al.⁽²⁰⁾ synthesized a series of methoxyphenethylamines containing an α -trifluoromethyl group. None of these compounds, however, was as potent as the methyl analogs.

Walters and Cooper⁽²¹⁾ prepared trans-2-(3,4,5-trimethoxyphenyl)cyclopropylamine (19) and found that it displayed mescaline-like activity. This compound was synthesized in an attempt to prolong the effects of mescaline, but it was found to have a shorter duration of activity.

Cooper later reported⁽²²⁾ stereospecific syntheses of cis- and trans-2-(3,4,5-trimethoxyphenyl)cyclopropylamine, but did not describe any pharmacology.

In addition to the methoxylated phenethylamines, several related phenethylamines have been found to possess psychotomimetic activity. Knoll et al.⁽²³⁾ studied the psychotomimetic properties of p-substituted-N-methylphenylisopropylamines. These compounds were reported to possess the following activities: p-amino (20a), 6 M.U.; p-nitro (20b), 28 M.U.; p-iodo (20c), 8 M.U.; p-chloro (20d), 27 M.U. and p-bromo (20e), 20 M.U. Similar substitutions of the meta-position of phenylisopropylamine yielded potent psychostimulants which were devoid of psychotomimetic activity.



(20)

R = NH₂ (20a)

R = NO₂ (20b)

R = I (20c)

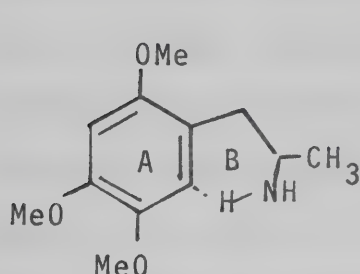
R = Cl (20d)

R = Br (20e)

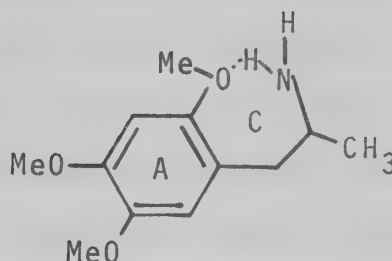
Theories concerning the criteria that substituted phenethylamines require to possess psychotomimetic activity have been postulated. These theories compare phenethylamines with LSD. Since LSD is the most potent of the known hallucinogens and because it is a rigid structure, it serves as a suitable model for comparison.

Snyder and Richelson⁽²⁴⁾ theorized that the phene-

thylamines are capable of forming the pseudo ring structures (21, 22) which resembled the A/B and A/C rings of LSD.



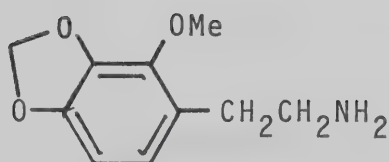
A/B conformation (21)



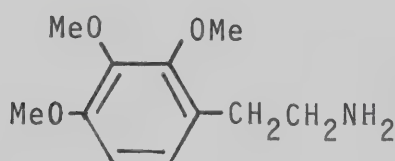
A/C conformation (22)

These workers postulated that the ability of the phenethylamines to form such bonded structures was critical so far as hallucinogenic activity was concerned. The ability of the phenethylamine derivatives to form the bonded conformation A/C of LSD (see structure 22) necessitates the presence of a methoxy group at the ortho-position. This methoxy group must be free to rotate so that it can adopt the spatial position necessary to form the bonded seven-membered ring C. If an additional methoxy group is placed on the ring position next to this ortho-substituent, a decrease in activity usually results. This adjacent methoxy group supposedly sterically hinders the ortho-substituent from adopting the required spatial position essential for formation of a seven-membered ring. Structures methoxylated at the ortho-position and containing a meta-substituent which is part of a methylenedioxy group, such as 2-methoxy-3,4-methylenedioxyphenethylamine (23), 5 M.U., retain their

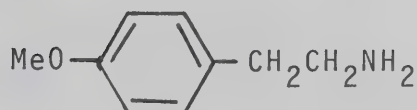
activity. In accord with this theory, the 3,4-methylene-dioxy group would be fixed in space well removed from the 2-methoxy-substituent, and therefore would not hinder the latter's free rotation. The related compound, 2,3,4-trimethoxyphenethylamine (24) is much less active, as would be expected from this theory. The activity of many of the analogs in Table I can be predicted surprisingly well by means of the Snyder-Richelson postulate. However, this theory is not applicable to all the phenethylamine psychotomimetics. For example, 4-methoxyphenethylamine (25) has been reported to be as active as mescaline⁽⁵⁾ even though it obviously cannot form the A/C conformation (22).



(23)



(24)



(25)

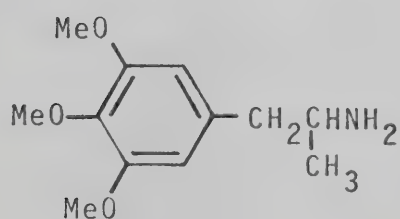
Although mescaline also cannot form the A/C conformation (22), it is capable of forming an intramolecularly bonded structure reminiscent of ring B of LSD. It has been shown by negative π charge calculations^(25,26) that, of all the possible trimethoxylated analogs, mescaline had the greatest charge at the 2- and 6-ring positions. This would facilitate formation of an A/B conformation. A correlation between the tendency of several methoxylated phenethylamines to form A/B and A/C ring conformations corresponding to LSD and their experimentally determined activity has been summarized⁽²⁷⁾ and is reproduced in Table II.

Table II

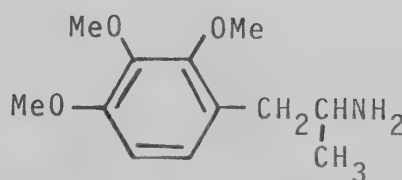
Tendency of Methoxylated Phenethylamines
to Form A/B or A/C Ring Conformations of LSD

Compound	Tendency to Form		Potency, Mescaline Units
	Ring B	Ring C	
2,4,6-Trimethoxy	0	4	10
2,4,5-Trimethoxy	0.7	2	17
6-Methoxy-3,4-methylenedioxy	0.7	2	21
2-Methoxy-3,4-methylenedioxy	0.6	2	18
2,3,6-Trimethoxy	0	2	<10
3,4,5-Trimethoxy	2	-	2.2
3-Methoxy-4,5-methylenedioxy	2	-	2.7
2,3,5-Trimethoxy	1	0	<7
2,3,4-Trimethoxy	0.6	0	<2

Snyder and Merrill^(25,26) undertook molecular orbital calculations on a variety of psychotomimetic drugs as well as their non-psychotomimetic counterparts. They found a relationship between electronic configuration and activity. They also calculated the energy of the highest occupied molecular orbital for a series of mono-, di-, and tri-substituted phenethylamines. Their results showed that progressive methoxylation resulted in an increase in the energy of the highest occupied molecular orbital (E_H). Mescaline, interestingly, was found to have the highest occupied molecular orbital energy in the trimethoxylated phenethylamine series. Similar calculations on a series of 1-(trimethoxyphenyl)isopropylamines revealed that the energy of the highest occupied molecular orbital was greatest for 1-(2,4,5-trimethoxyphenyl)isopropylamine (10a), 17 M.U.; 1-(3,4,5-trimethoxyphenyl)isopropylamine (26a) was intermediate, 2.2 M.U.; and the lowest was 1-(2,3,4-trimethoxyphenyl)isopropylamine (26b), <0.2 M.U. Calculations made on chemically unrelated compounds such as LSD and psilocin showed excellent relationships between theoretical and observed potencies.



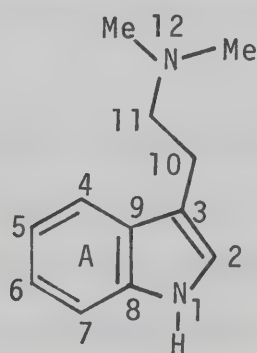
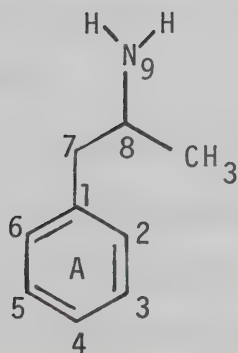
(26a)



(26b)

This correlation between the energy of the highest occupied molecular orbitals and psychotomimetic activity suggests that part of the psychedelic molecule functions as an electron donor at its site of action.

Kang and Green⁽²⁸⁾ have commented on the feasibility of phenethylamines forming bonded rings A/B and A/C (21, 22) of LSD as described by Snyder and Richelson⁽²⁴⁾. They stated that such structures would be very unstable and doubted if they even existed. They reasoned that ring C would not be formed because at biological pH the amine would be protonated and would tend to react with counter ions. Alternatively, they suggested that ring A and the N-6 nitrogen atom of LSD are essential for psychotomimetic activity, these being two important sites which react with the receptor. They postulated that the amphetamines and indole-alkylamines exist at the receptor site in a preferred conformation which permits the benzene ring to lie like ring A of LSD and the alkylamine nitrogen atom to take up a position equivalent to the N-6 nitrogen atom of LSD.



Hence ring A could interact with the receptor forming a molecular complex as suggested by the correlation between hallucinogenic activity and the energy of the highest occupied molecular orbital. It was thought the N-6 nitrogen atom of LSD or the aliphatic nitrogen atom of the other hallucinogens might react with the receptor forming a donor acceptor complex of the $n-\pi^*$ or $n-G^*$ type. They further suggested that the methoxy and hydroxy groups of amphetamines and indolealkylamines as well as the pyrrole ring of LSD and indolealkylamines were sterically unimportant and act to confer a high E_H which is a requirement for hallucinogenic activity.

The absolute configuration of biologically active LSD is known⁽²⁹⁾. The aromatic indole ring is planar, and the two alicyclic rings are puckered. The asymmetric center, C-5, is above the aromatic plane, while the diethylamide group at C-8 is in the equatorial position. Molecular models suggest that the N-6 is below or near the aromatic plane and the C-7 is above the plane. As the N-methyl group can assume the equatorial position, the lone-pair electrons at the N-6 nitrogen are below the aromatic plane.

Kang⁽²⁸⁾ reasoned that if the interaction between the N-6 nitrogen atom and the receptor was an electrostatic one, the inactive L-form of LSD might be expected to have activity since the charge on the nitrogen atom is spread.

In a donor-receptor type of complex, the lone pair of electrons of the D-form would be near the receptor if it is below the plane, whereas in the L-form, the lone pair of electrons would be above the plane.

The amino group of the 2-aminoindanes prepared in the present study is fixed in a position similar to that described for the N-6 nitrogen atom of LSD. Depending on the pharmacological activity of these cyclic analogs, it may be possible to ascertain which of the two theories pertaining to psychotomimetic activity of phenethylamines is correct.

The Use of DOM (STP) as a Hallucinogen

Because a portion of this study involves the examination of possible active side products in a synthesis of DOM, a brief historical review of the use of DOM as a 'street drug' (STP) is relevant.

In the summer of 1967, 20,000 tablets of a hallucinogenic compound of unknown origin were distributed in San Francisco. The drug was called STP (serenity, tranquillity and peace) and press reports described it as being more potent and longer acting than LSD. The Food and Drug Administration⁽³⁰⁾ examined samples of STP and found they contained a chemical identical with the experimental drug 1-(2,5-dimethoxy-4-methylphenyl)isopropylamine which was developed by Dow Chemical and coded with the initials DOM.

Another sample of STP, thought to be of Californian origin, was also found to contain DOM⁽³¹⁾.

Initially there existed some confusion about the degree and duration of the effects of this drug. Solursh⁽³²⁾ reported that the effects of STP were four to seven days in duration. Louria, in two reports^(33,34), also observed that STP was similarly long acting. Snyder and his co-workers^(35,36) undertook a detailed clinical study of pure DOM. In disagreement with Solursh and Louria, they found that the effects of the drug lasted only about eight hours. They reported that psychotomimetic effects occurred at doses greater than 5 mg. When doses greater than 10 mg [the average dose of 'street STP'⁽³⁷⁾] were administered, the effects were not observed to extend beyond 24 hours. Other clinical studies⁽³⁷⁻³⁹⁾ undertaken with DOM showed that the threshold dose of the drug in adults was 2 mg. Doses above 5 mg produced psychotomimetic effects. The subjective effects of DOM began 1 to 1 1/2 hours after its administration. Peak intensity occurred after 3 to 4 hours, then subsided by 5 to 6 hours. Prolonged activity was not reported to occur; therefore, it would appear that the reports⁽³²⁻³⁴⁾ of the long lasting effects of STP are questionable.

Snyder⁽³⁵⁾ suggested that the "hippie" population who developed prolonged reactions to STP may have been sensitized by previous experiences with hallucinogenic drugs.

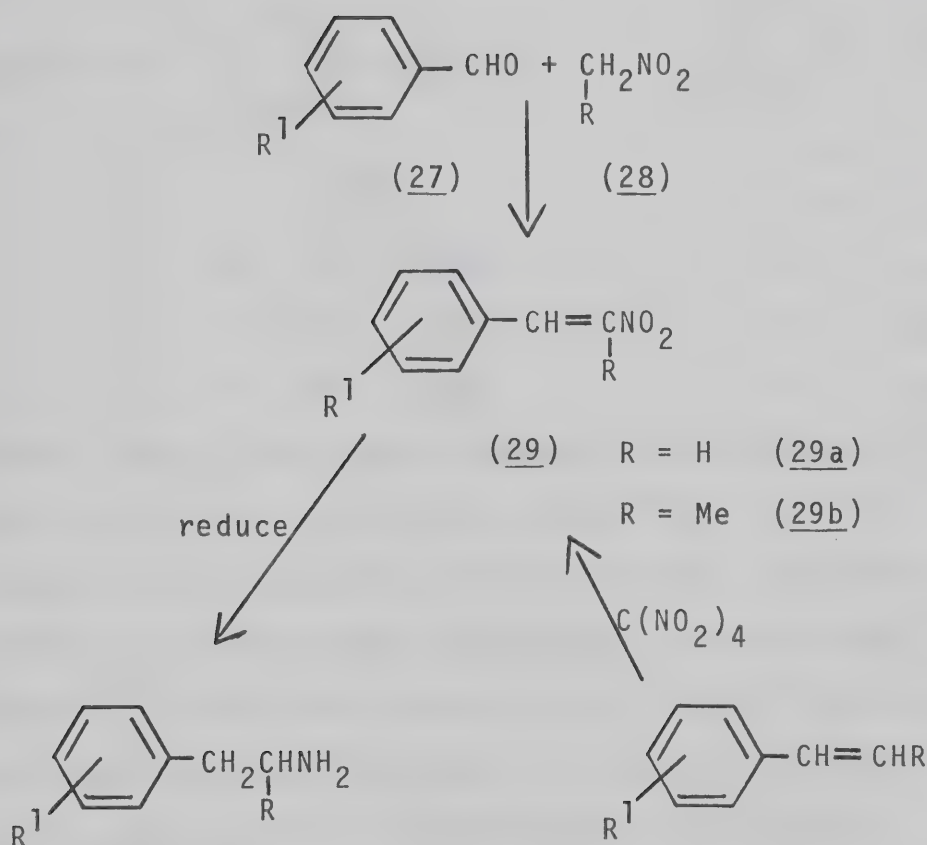
Faillace⁽³⁷⁾ has commented that the degree of hallucinogenic reaction is influenced by the drug, its dose, the environment in which it is taken, and the emotional stability of the individual taking the drug.

An alternative explanation for the observed long lasting effects of STP is the possibility that several different compounds have been called STP or that some samples of STP contained more than one component. Phillips and Mesley⁽³¹⁾, in addition to finding DOM in a sample of STP, also found several unidentified components. However, these additives did not alter the activity of STP relative to a pure sample of DOM.

The Synthesis of Phenethylamines

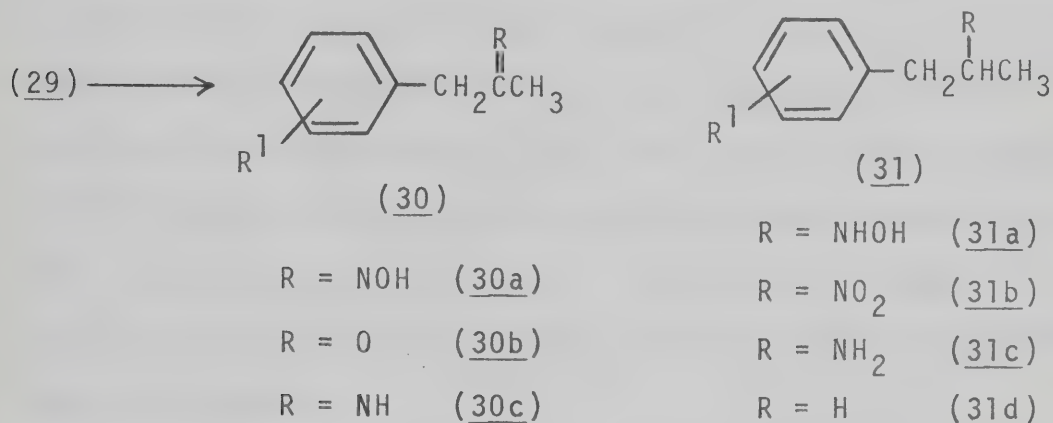
The preparation of phenethylamines has been undertaken by a variety of methods, but the most useful preparative route has been the reaction between an appropriately substituted aldehyde and a nitroalkane (27 and 28). The reaction of aldehydes with nitromethane or nitroethane employing varied reaction conditions has given excellent yields of nitroalkenes (29a, 29b)^(12,17,18,40). Nitroalkenes (29) have also been obtained from the reaction of a suitable styrene with tetranitromethane^(11,40). Reduction of the nitroolefins to the corresponding phenethylamines is usually accomplished with lithium aluminum hydride (LAH)^(12,17,41-45). This reduction has also been successfully conducted

with amalgamated zinc and hydrochloric acid⁽⁴⁶⁾, zinc and acetic acid^(47,48), aluminum amalgam⁽⁴⁷⁾, palladium and hydrogen in an acetic-sulfuric acid solvent⁽⁴⁹⁾, and with Raney nickel and hydrogen⁽⁵⁰⁾. These reactions are summarized in Scheme 1.



Scheme 1

A variety of products other than the phenethylamines has been isolated following treatment of the nitropropenes⁽²⁹⁾ under various reducing conditions. For example, when these structures (29) were reduced with iron and hydrochloric acid, depending on the concentration of hydrochloric acid, they yielded either a ketone (30b) or the corresponding oxime (30a)⁽⁵¹⁾. A similar reaction has been reported by Shepard *et al.*⁽⁵²⁾.



Ketones (30b) have been recovered after treating nitropropenes (29) with iron, water, and sulfuric acid⁽⁵³⁾.

Reductions of nitropropenes with stannous chloride have yielded α -methoxyoximes, saturated nitro compounds, and oximes⁽⁵⁴⁾, while the reduction of 1-phenyl-2-nitropropenes with hydrazine and platinum or palladium was reported⁽⁵⁵⁾ to be a good method of preparing the imine (30c). When nitropropenes were reduced at 15° to 40° over platinum or palladium at 15 to 500 psi, the nitropropane (31b), the ketone (30b) and the oxime (30a) were isolated. Tindall⁽⁵⁶⁾ reported the production of amines and ketones when nitro-

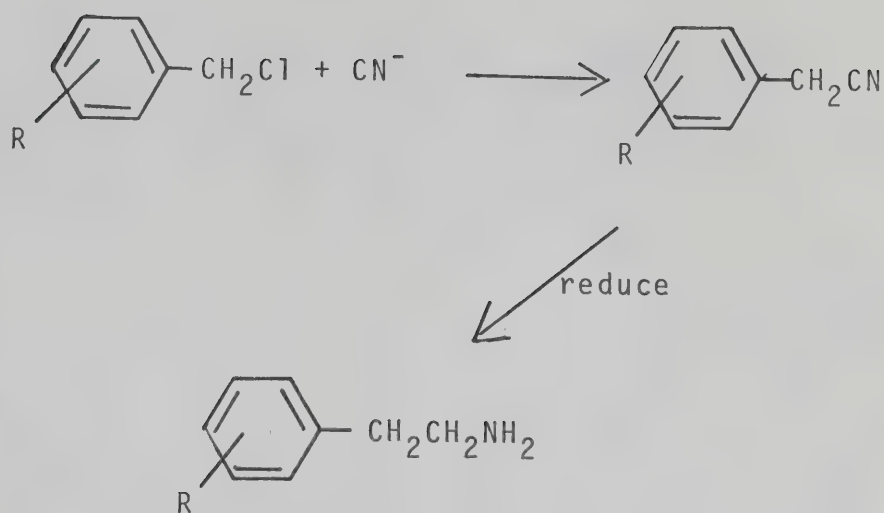
olefins were reduced at high pressures in the presence of Raney nickel. The presence of formic acid resulted mostly in ketone formation and only a small amount of amine⁽⁵⁷⁾. Various products were obtained from the reduction of 1-phenyl-2-nitropropene by the inverse addition of lithium aluminum hydride^(58,59). These consisted of the amine (31c), structures (30a - 30c), as well as (31a) and (31b).

In addition to the methods which employ nitroölefins as precursors, several other synthetic procedures have been used to prepare phenethylamines. A successful method⁽⁶⁰⁻⁶⁴⁾ involved the conversion of the appropriate benzyl chloride to the corresponding cyanide which was then reduced to the amine as outlined in Scheme 2. These latter compounds are also accessible by means of the Hoffmann rearrangement⁽⁶⁵⁻⁶⁸⁾ shown in Scheme 3.

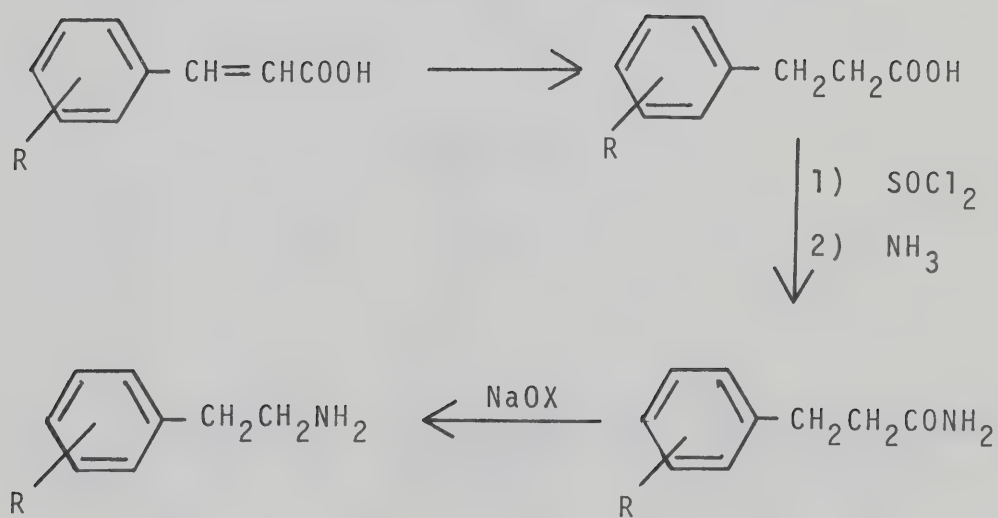
Rabusic and Gregor⁽⁶⁹⁾ prepared mescaline using the synthetic route shown in Scheme 4. Other synthetic routes such as those shown in Schemes 5, 6, and 7 have also provided the desired amines. Beta-substituted phenethylamines have been prepared by alternative routes (Schemes 8 and 9).

Phenethylamino Acids

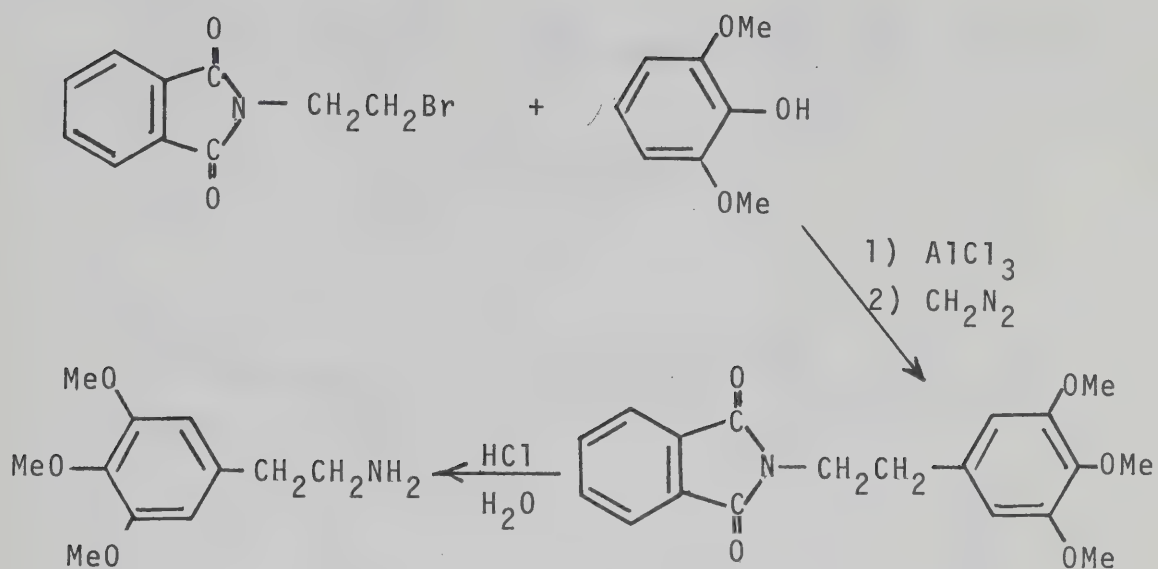
Several substituted phenylalanines were prepared to determine whether they possessed psychotomimetic properties. A brief survey of the literature pertinent to this study



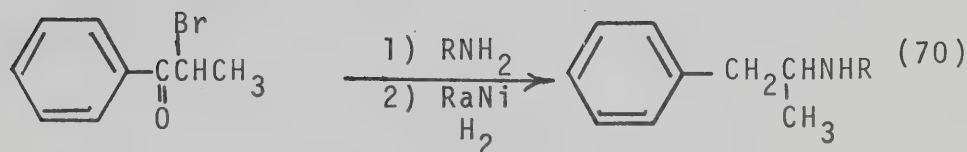
Scheme 2



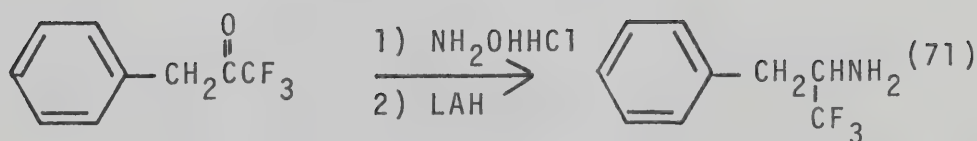
Scheme 3



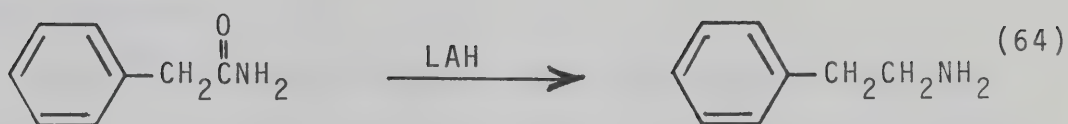
Scheme 4



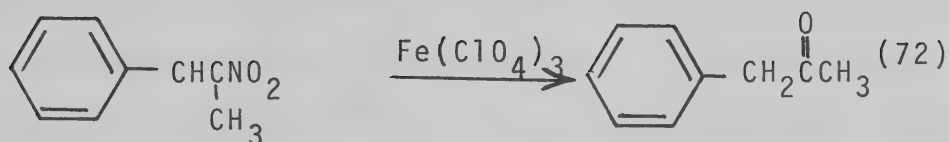
Scheme 5



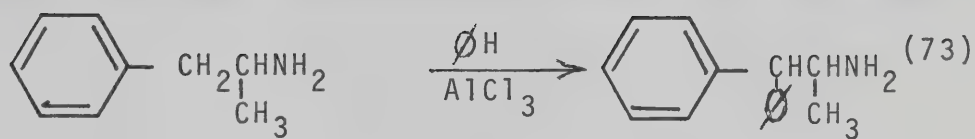
Scheme 6



Scheme 7



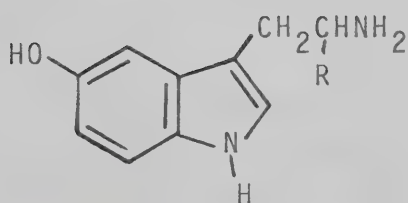
Scheme 8



Scheme 9

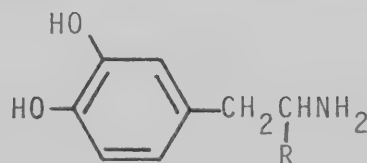
is now presented.

Boyd⁽⁷⁴⁾ studied tissue concentrations of labelled mescaline in rats and cats and found that the brain contained the least amount of the administered dose. Denber and Teller⁽⁷⁵⁾ found that <0.002 parts of an intravenously injected dose of mescaline was taken up by the CNS of young rats. A maximum of 0.14% of the dose in the brain was attained in 30 minutes⁽⁷⁶⁾. For a drug to possess psycho-active properties, it must pass the blood-brain barrier. The ability of materials to pass this theoretical barrier varies with the oil/water partition-coefficient of the material in question. Since the blood-brain barrier is highly lipid in nature, polar substances do not readily pass into the brain⁽⁷⁷⁾. Several groups of compounds, including amino acids, are actively transported into the brain⁽⁷⁸⁾. 5-Hydroxytryptophan (32b) and 3,4-dihydroxyphenylalanine (33b), for example, pass the blood-brain barrier much more rapidly than the corresponding amines (32a) and (33a)^(79,80).



R = H (32a)

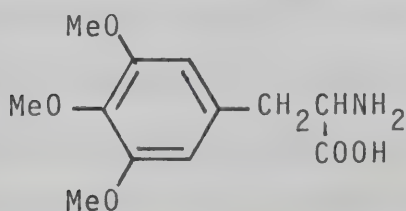
R = COOH (32b)



R = H (33a)

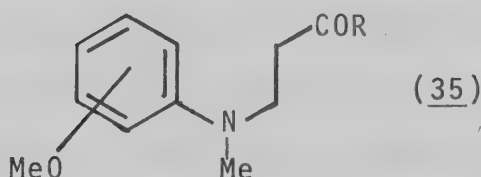
R = COOH (33b)

In an attempt to increase the brain levels of mescaline, the corresponding amino acid, namely 3,4,5-trimethoxyphenylalanine (34), was prepared⁽⁸¹⁾. It was rationalized that this compound, since it was an amino acid, would rapidly enter the brain, then be enzymatically decarboxylated to yield mescaline within the CNS. No pharmacological data were reported, and although it was stated that the pharmacological result would be published at a later date, no such publication has appeared. Smythies⁽⁸²⁾ pharmacologically evaluated 3,4,5-trimethoxyphenylalanine and reported that it was completely inactive as a psychotomimetic agent. It was suggested that this material (34), based on a study of enzyme decarboxylase substrate specificity by Ferrini and Glasser⁽⁸³⁾, was a poor substrate for the decarboxylase enzyme and hence mescaline was not formed in the brain. This study showed that all the isomers of DOPA (dihydroxyphenylalanine) were good substrates for mammalian DOPA decarboxylase enzyme, while phenylalanines substituted with two methoxyl groups failed to be decarboxylated by the decarboxylase enzyme.

(34)

Although 3,4,5-trimethoxyphenylalanine has been reported elsewhere in the literature⁽⁶⁹⁾, it was prepared only as a synthetic intermediate. A variety of other substituted phenylalanines, some resembling the known hallucinogens, have also been reported^(84,85) but no mention has been made of their possessing psychotomimetic activity.

Other amino acids, patterned after some structural aspect of LSD, have been prepared and evaluated for LSD-like activity. Liska *et al.*⁽⁸⁶⁾ prepared some ethyl esters, simple amides, and *N,N*-diethylamides of *N*-methyl-*N*-para-(*meta*)methoxyphenyl- β -alanine (35).



R = O-alkyl

R = NR₂

R = N(Et)₂

Some of these compounds showed antiserotonin activity on the isolated rat fundus preparation. Later, Liska *et al.*⁽⁸⁷⁾ reported an absence of LSD-like activity in a series of pyridylethyl derivatives of β -alanine.

Leonard and Liska⁽⁸⁸⁾ also prepared some ethyl esters and *N,N*-diethylamides of β -alanine which were structurally related to the A/D ring portions of LSD. These compounds were evaluated and little similarity was found between their effects and those of LSD.

Metabolism of Phenethylamines

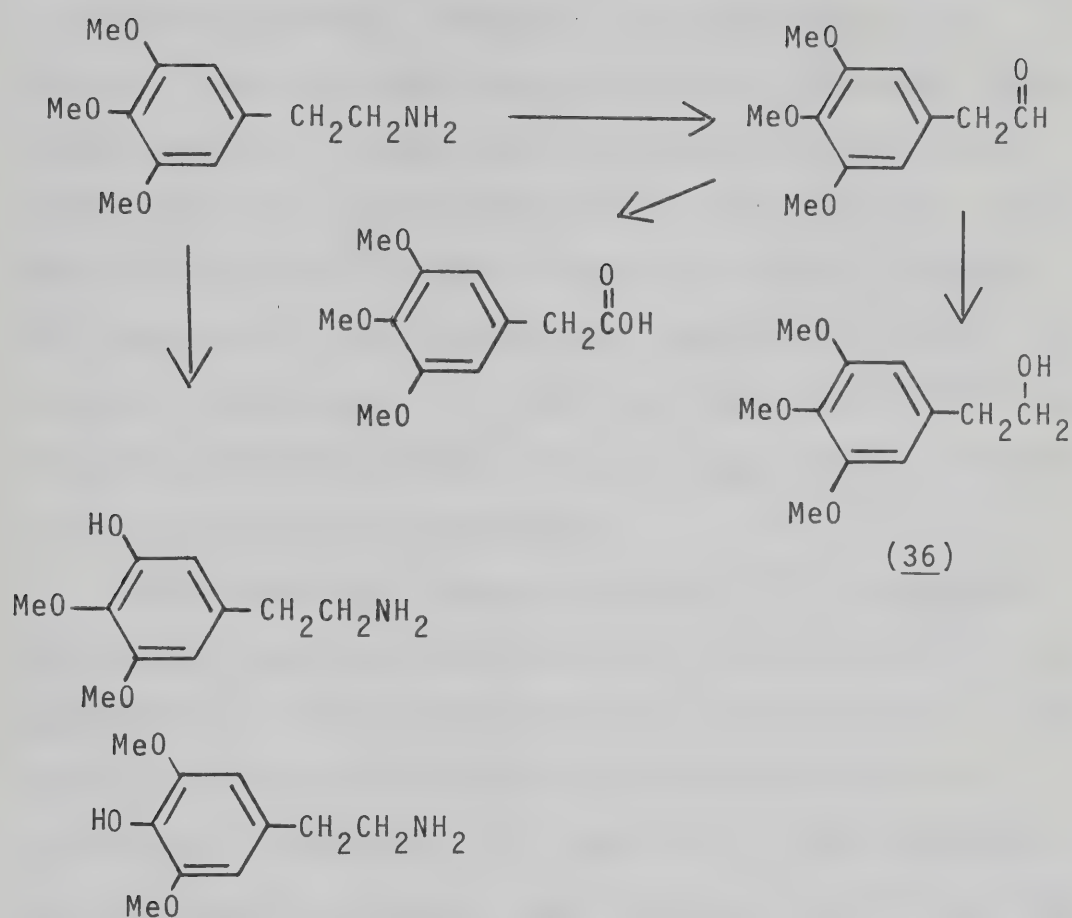
As stated earlier, a section of the present study involves the synthesis of some possible metabolites of DOM; for this reason the following summary of metabolic studies of similar compounds is presented.

Extensive metabolic studies⁽⁸⁹⁻⁹⁵⁾ have shown that mescaline is detoxified by three routes, i.e. demethylation, oxidative deamination, and conjugation. The major pathways, which are species dependent, are shown in Scheme 10.

Friedhoff and Goldstein⁽⁹⁰⁾ undertook a study of the action of mescaline, and their experimental results suggested that its psychotomimetic activity was due to a metabolite, namely 2-(3,4,5-trimethoxyphenyl)ethanol (36).

The metabolism of 3,4-dimethoxyphenethylamine has been reported^(96,97); the metabolites formed were 3,4-dimethoxyphenylacetic acid, 2-(3,4-dimethoxyphenyl)ethanol, N-acetyl-3,4-dimethoxyphenethylamine, N-acetyl-3-methoxy-4-hydroxyphenethylamine, and 2-(3-methoxy-4-hydroxyphenyl)-ethanol. The relative amounts of each metabolite were 77, 0.1, 0.1, 6.2, and 0.1 percent respectively and 15.5% of the material was excreted as the free amine. This agreed with the observation of Sargent and colleagues⁽⁹⁸⁾ that demethylation of the 4-methoxy group was 15 times as rapid as the demethylation of the 3-methoxy group.

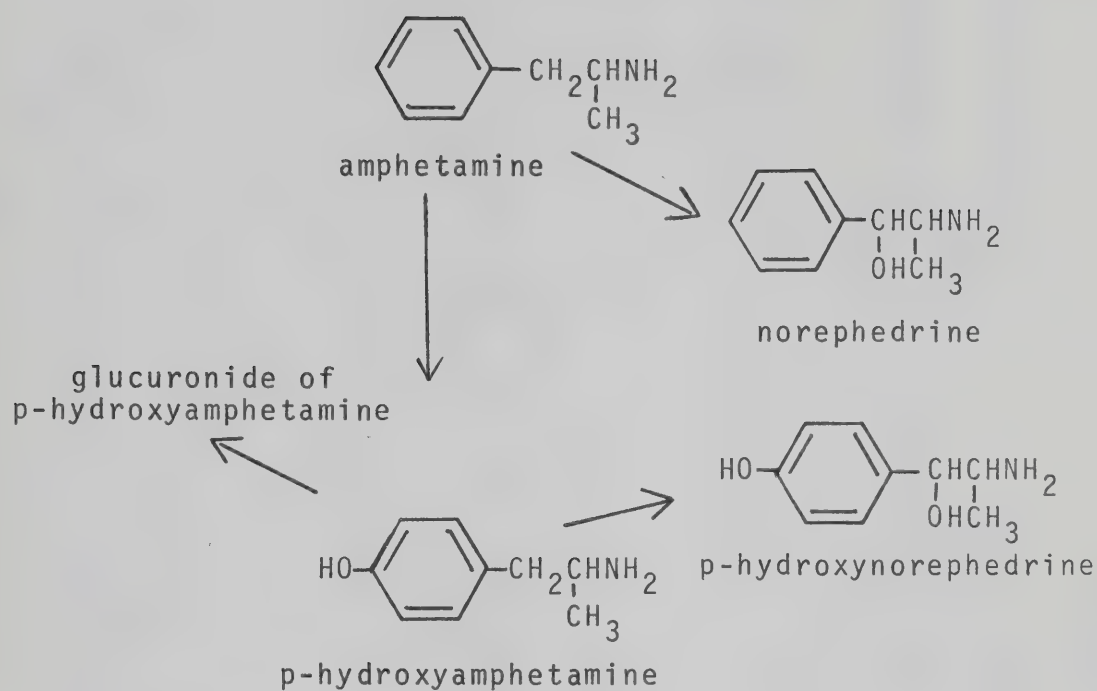
The metabolism of α -methylphenethylamine (amphetamine) has been reviewed by Smith and Dring⁽⁹⁹⁾. They summarized



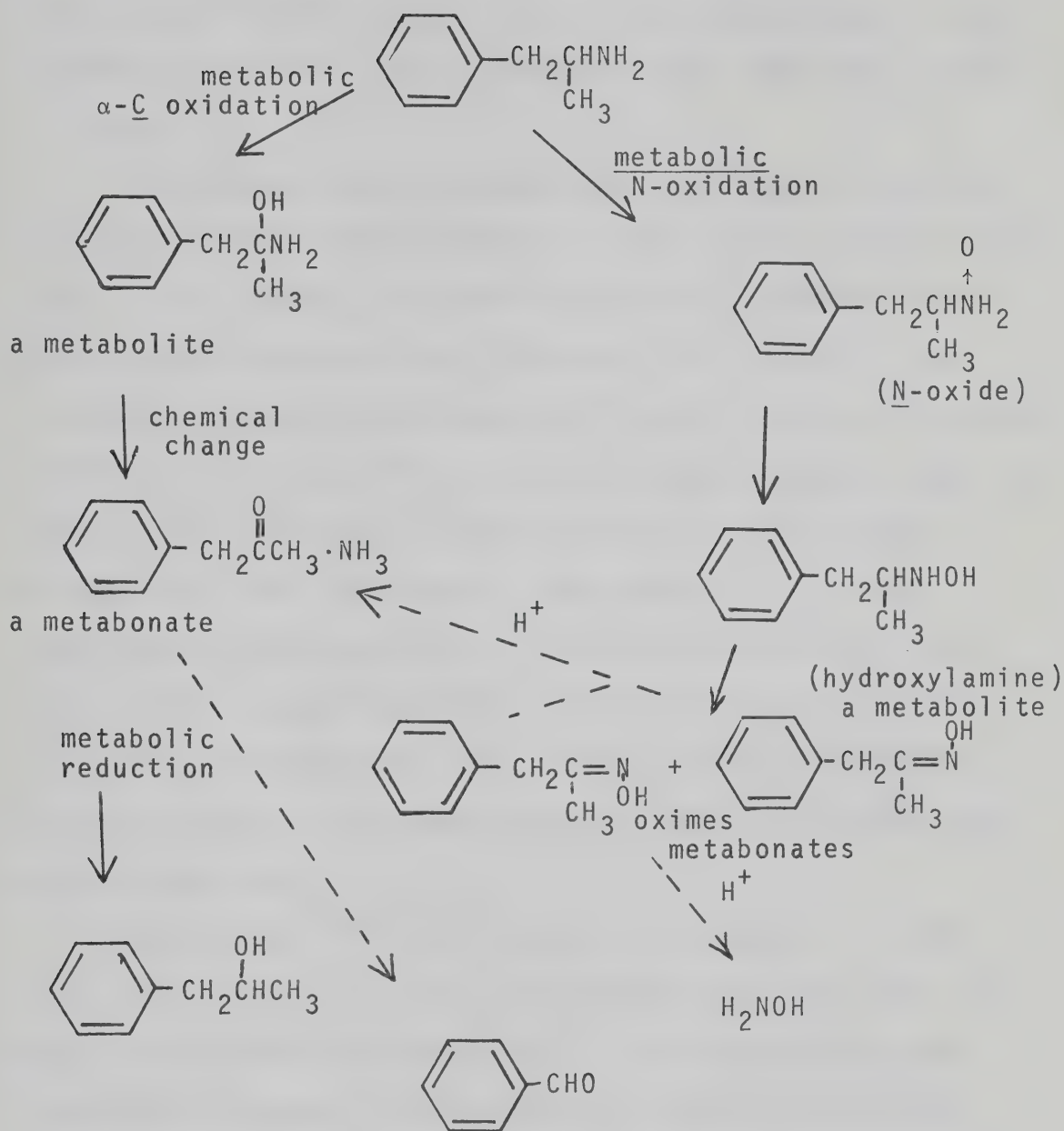
Scheme 10

the various routes of detoxification of amphetamine as shown in Scheme 11 and 12. The metabolism of amphetamine is species dependent. Rabbits and guinea pigs, for instance, detoxify amphetamine mainly by oxidative deamination, while the major reaction in the rat is aromatic p-hydroxylation. In the case of the dog and mouse, ring hydroxylation and oxidative deamination occur to about the same extent. Man metabolizes amphetamine largely by oxidative deamination. It was also reported by Smith and Dring that N-hydroxylation did not appear to be involved in the metabolism of amphetamine.

More recently, however, Beckett⁽¹⁰⁰⁾ suggested a mechanism involving N-oxidation in the formation of some intermediates in the detoxification of amphetamine. The sequence of steps in the detoxification reaction is reproduced in Scheme 13. In addition to phenylacetone and its corresponding alcohol, syn- and anti-oximes have been reported as intermediates in the metabolism of amphetamine and a number of ring substituted amphetamines, e.g. 3,4-methylenedioxyamphetamine. The oximes were not considered to be primary metabolites, but rather, as was phenylacetone, the result of a chemical change. These were termed metabolites and were inferred to originate from the primary metabolites as shown in Scheme 13. The hydroxylamine derivative of amphetamine, contrary to the findings reported in the previously mentioned reference, was detected.



Scheme 11



Scheme 13

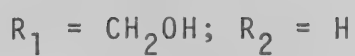
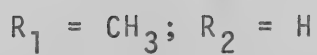
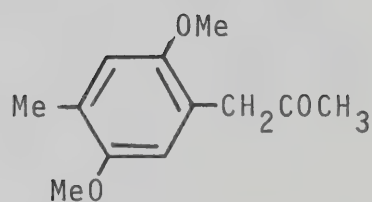
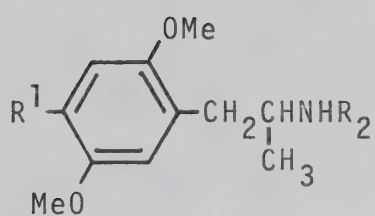
Ho and Tansey⁽¹⁰¹⁾ undertook the study of the metabolism of DOM in rats. To assist in the identification of the metabolites, they synthesized the compounds listed in Table III.

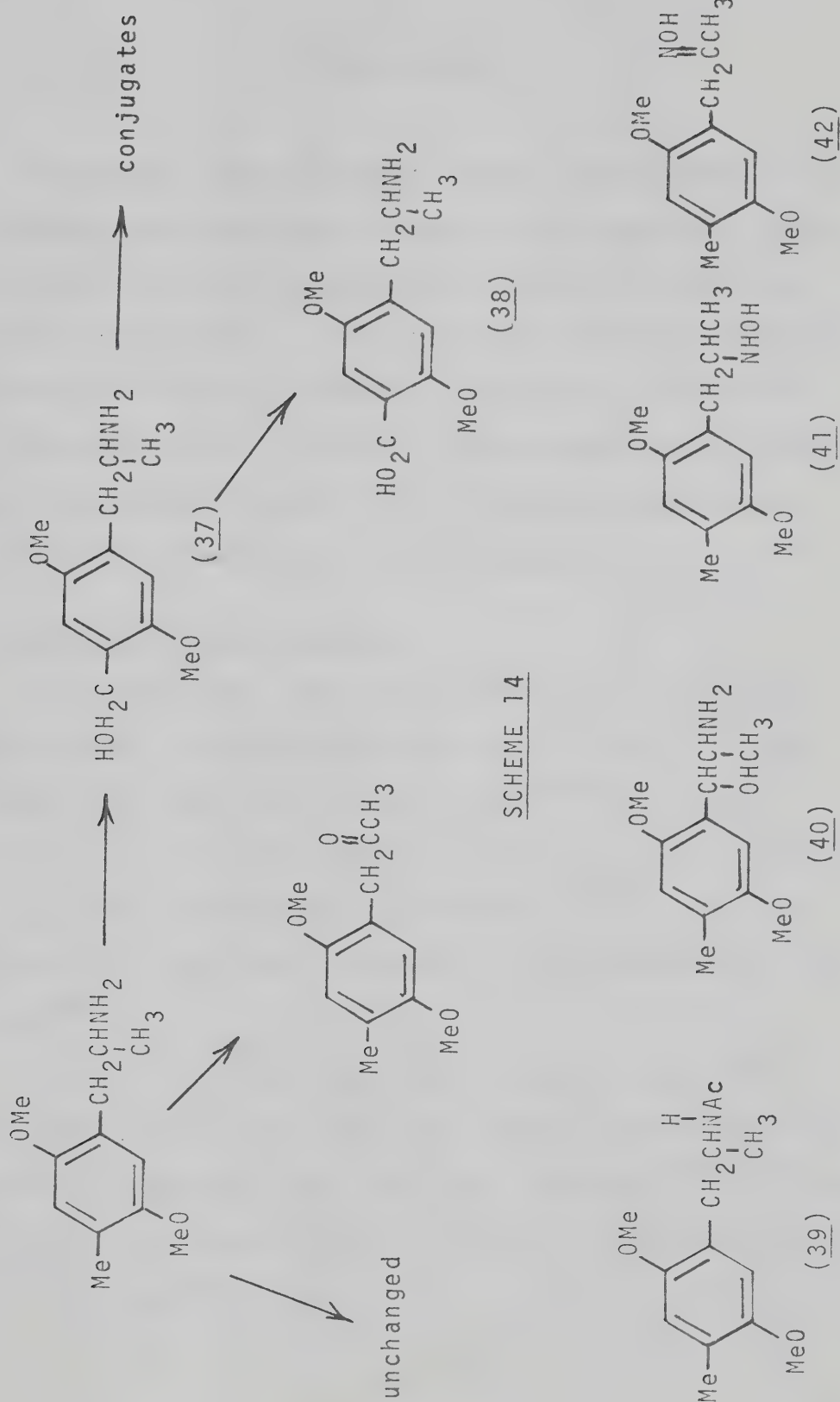
The major route of metabolism was found to be the oxidation of the 4-methyl group to the corresponding alcohol (37). This alcohol, free and conjugated, accounted for 50% of the metabolites in a 24-hour urine sample. The 4-carboxy compound (38) accounted for 28%, and the unchanged form was found to be 8% of the administered dose. The same authors⁽¹⁰²⁾ described ³H-labelled metabolites of DOM in 24-hour rat urine and feces. They found 62.7% of the administered radioactivity in the urine and 20.2% in the feces. They summarized their results in the manner shown in Scheme 14. Compounds (39) and (40) were not detected. The formation of the hydroxylamine (41) or the oximes (42) was not mentioned.

Ho et al.⁽¹⁰³⁾ investigated the uptake of ³H-DOM into rat and monkey brains. Although they found that the metabolism of DOM occurred rapidly, no metabolites were found to be present in the brains of rats and only very little appeared in monkey brains. This study showed that the psychotomimetic activity of DOM was due to the parent compound and not a metabolite.

Table III

Possible Metabolites of DOM





II.

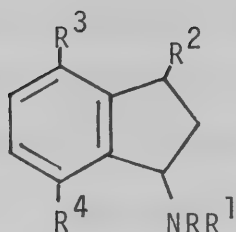
AMINOINDANES

The second major purpose of the present study was to investigate the properties of some cyclic compounds which are related to the phenethylamines, namely substituted 1- and 2-aminoindanes. These compounds, although they are not known to be hallucinogenic, do possess a variety of other pharmacological effects. The pharmacology of some compounds structurally similar to those synthesized and reported in this thesis is now presented.

Pharmacology of 1-Aminoindanes

The amines (43 - 46) have been found to possess antidepressant and psychostimulatory activity⁽¹⁰⁴⁾ and compounds (47) and (48) are described⁽¹⁰⁵⁾ as useful in the treatment of anxiety neurosis and depression. Compounds (49 - 51) were found to be vasodilators⁽¹⁰⁶⁾. Similar compounds have also been prepared but no pharmacology was reported⁽¹⁰⁷⁾.

Various 1-substituted-3-aminoindanes have been synthesized⁽¹⁰⁸⁻¹¹⁰⁾ and some have been pharmacologically evaluated. Compounds (52 - 57), for instance⁽¹¹¹⁻¹¹²⁾ were found to dilate blood vessels, and to have spasmolytic and anesthetic properties.



$$R = R^2 = R^3 = R^4 = H; R^1 = CH_2-C\equiv CH \quad (43)$$

$$R^2 = R^3 = R^4 = H; R = Me; R^1 = CH_2-C\equiv CH \quad (44)$$

$$R = R^2 = R^3 = R^4 = H; R^1 = Me \quad (45)$$

$$R = R^2 = R^3 = R^4 = H; R^1 = \text{cyclopentyl} \quad (46)$$

$$R = R^1 = R^2 = H; R^3 = Cl; R^4 = OMe \quad (47)$$

$$R = R^1 = Me; R^2 = H; R^3 = Cl; R^4 = OMe \quad (48)$$

$$R = R^1 = R^2 = R^4 = H; R^3 = \text{IsoProp.} \quad (49)$$

$$R = R^1 = R^3 = R^4 = H; R^2 = \text{Obutyl} \quad (50)$$

$$R = R^1 = R^3 = R^4 = H; R^2 = \text{Ohexyl} \quad (51)$$

$$R = R^3 = R^4 = H; R^1 = Me; R^2 = NHMe \quad (52)$$

$$R^3 = R^4 = H; R = R^1 = Me; R^2 = NH_2 \quad (53)$$

$$R^3 = R^4 = H; R = R^1 = Me; R^2 = NMe_2 \quad (54)$$

$$R = R^3 = R^4 = H; R^1 = Ph; R^2 = NMe_2 \quad (55)$$

$$R = R^3 = R^4 = H; R^1 = Ph; R^2 = NEt_2 \quad (56)$$

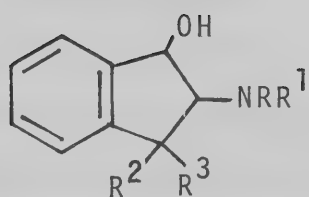
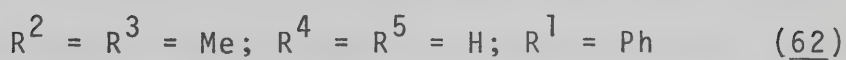
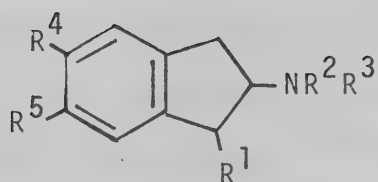
$$R^3 = R^4 = H; R = Me; R^1 = Ph; R^2 = NH_2 \quad (57)$$

Pharmacology of 2-Aminoindanes

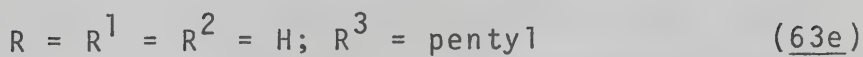
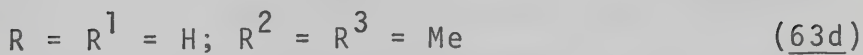
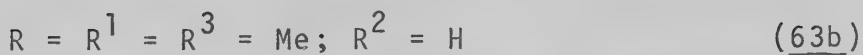
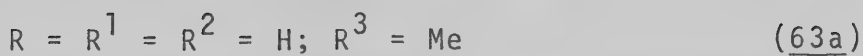
The parent compound (58), in addition to having cough suppressant and breathing stimulant properties⁽¹¹³⁻¹¹⁴⁾, is a potent analgesic⁽¹¹⁵⁾ which is synergistic with morphine. In an attempt to increase the analgesic activity of (58), various analogs of 2-aminoindane have been synthesized. Kameyama and Oyawagi⁽¹¹⁶⁾ and Kematani and Sugahara⁽¹¹⁷⁾ examined various N-substituted 2-aminoindanes; all were less potent than the parent structure. The two ring methoxylated analogs (59) and (60) were also found⁽¹¹⁸⁾ to be analgesics.

Levin et al.⁽¹¹⁹⁾ prepared some N-substituted derivatives of 2-aminoindane, 2-amino-1-indanol and 1-amino-2-indanol. Several of these compounds were active bronchodilators with little effect on blood pressure. Swanson⁽¹²⁰⁾ reported that 2-amino-1-indanol, at doses equivalent to effective doses of ephedrine, did not affect smooth muscle or have pressor action.

Richter and Schenck⁽¹²¹⁾ prepared structures (61) and (62), and found that they possessed analeptic activity. In an attempt to obtain compounds with bronchodilator properties, Heinzelmann⁽¹²²⁾ synthesized 36 methoxylated and methylenedioxy analogs of 2-amino-1-indanol and 2-amino-1-indane, and found⁽¹²³⁾ that 2-methylamino-1-indanol and its benzyl ether possessed this activity. Heinzelmann further prepared some methoxy- and hydroxy-substituted



(63)



2-aminoindanols^(124,125) and showed that they relaxed constricted bronchi and affected blood pressure. Tanke et al.⁽¹²⁶⁾ prepared some methoxylated cis- and trans-2-amino-1-indanols; they, however, did not report any pharmacology.

Richler and Schenck⁽¹²⁷⁻¹³⁰⁾ investigated compounds of the general structure (63). Compounds (63a - 63c) were found to be active as analgesics, while 2-amino-1-phenylindanones and 2-amino-1-phenylindanols stimulated the CNS with no sympathomimetic action.

Numerous structures related to LSD, many of which are derivatives of 1,2,3,4-tetrahydro-2-naphthylamine, have been reported in the literature. Some of these compounds showed sympatholytic and oxytocic activities. A review article on this subject has recently been published⁽¹³¹⁾.

Chemistry of Aminoindanes

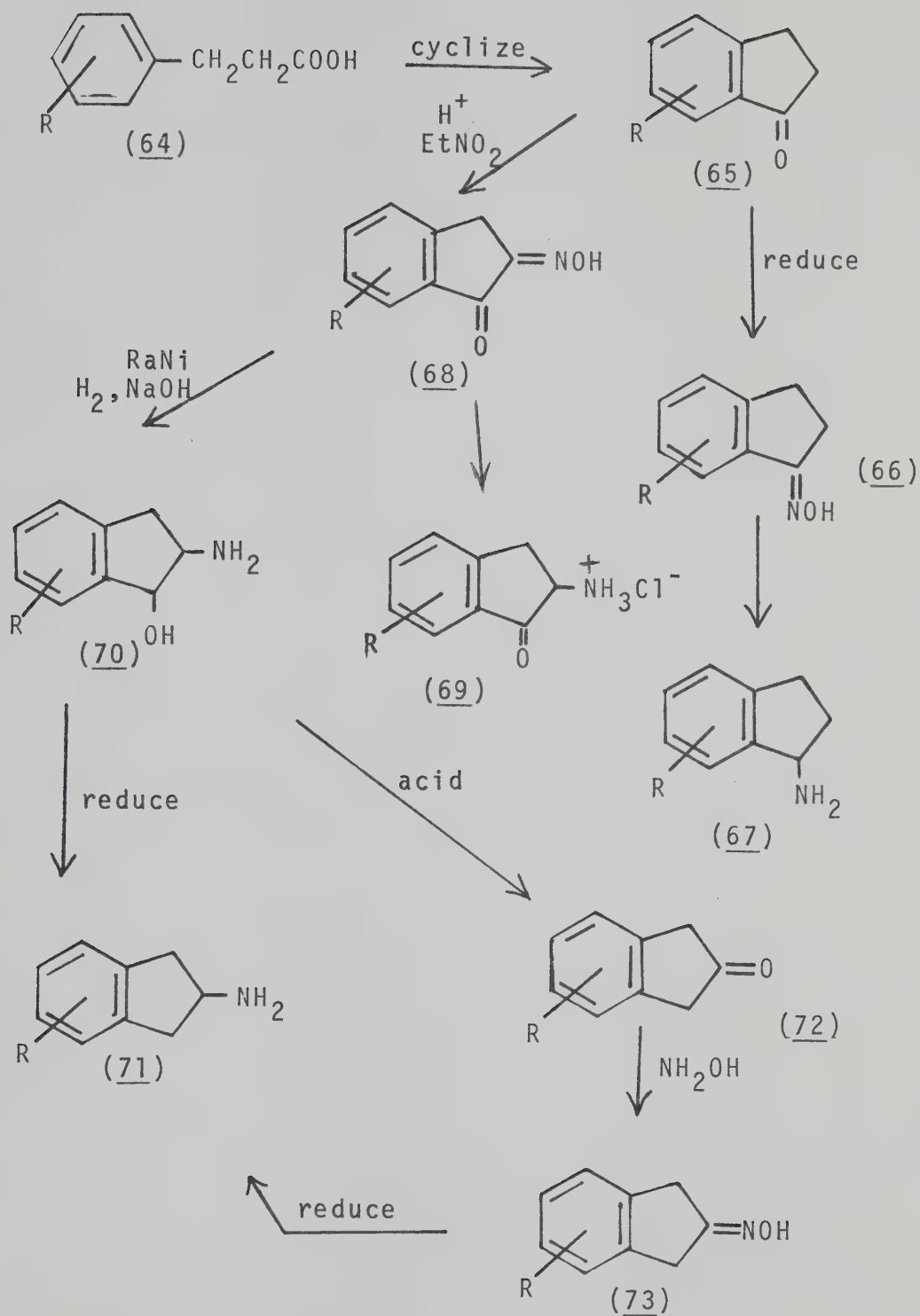
A typical preparative route to aminoindanes would employ a 3-phenylpropionic acid (64) as a starting material. This acid can be cyclized to a 1-indanone (65). This cyclization has been accomplished by employing a variety of agents including phosphorus pentoxide⁽¹³²⁾, sulfuric acid⁽¹³³⁾, phosphorus oxychloride⁽¹³⁴⁾ and polyphosphoric acid⁽¹³⁵⁾. 1-Indanones have also been prepared by treating phenylpropionylchlorides with aluminum chloride⁽¹³⁶⁾.

1-Aminoindanes (67) can be synthesized from 1-indanones. This involves formation of the oxime of the 1-indanone (6) followed by catalytic reduction.

2-Aminoindanes (71), although less accessible than 1-aminoindanes, are also prepared from 1-indanones. Treatment of 1-indanones with an alkyl nitrite such as butyl nitrite or ethyl nitrite results in the formation of a 2-isonitroso-1-indanone (68)^(118,121,124,125). This material can then be reduced to give a variety of 2-aminoindanes and simple derivatives by employing different reduction conditions. For instance, 2-amino-1-indanone hydrochloride (69) is obtained by hydrogenating 2-isonitroso-1-indanone in ethanolic hydrochloric acid^(124,125), while reducing the same starting material with hydrogen in a solvent containing sodium hydroxide and Raney nickel produces 2-aminoindanols, (70)^(111,128,130). These latter products when hydrogenated further in sulfuric acid-acetic acid in the presence of palladium and at 60°C yield the corresponding 2-aminoindanes (71)^(118,121).

2-Aminoindanes are also prepared from 2-indanones (72) in a manner similar to that employed for the synthesis of 1-aminoindanes. This preparation involves formation of the oxime (73) which is then reduced to the amine. The required 2-indanones can be prepared by treating 2-amino-1-indanols with acid^(126,137-139).

The series of reactions described is summarized in Scheme 15.



Scheme 15

DISCUSSION

I. PHENETHYLAMINES

a) Preparation and Properties of 1-(2,5-Dimethoxy-4-substituted phenyl)isopropylamines

A review of the structure-activity relationship studies of psychotomimetic phenethylamines has been presented in the literature survey. These studies show that the most potent psychoactive drugs of this chemical class are the ring methoxylated phenylisopropylamines. Two compounds of this latter class are much more active than any other member of this group. These compounds are shown by the general structure (10) in which R = Me and Et (i.e. compounds 10c and 10d). The former compound (10c) is also known as DOM and has gained a wide reputation as a 'street hallucinogen' under the name STP (serenity, tranquillity and peace). A third compound fitting this general structure is the p-bromo compound (10e) which has recently been prepared and investigated pharmacologically^(15,16). Preliminary reports indicate that this compound is also a very potent psychoactive drug. The derivative shown by structure (10) in which R = H (10f) has been found to be a moderately active psychedelic agent⁽⁵⁾.

Although only five different compounds of the general structure (10) have been prepared and evaluated pharmacologically, it appears that this ring substitution pattern may be important for psychotomimetic activity. To support or negate this premise, the preparation of

additional compounds with general structure (10) in which R = Cl, Br, and I (10g, 10e, 10h) was undertaken. The synthesis of the bromo-analog (10e) had been completed prior to its recent appearance in the literature.

The synthetic approach most commonly employed to prepare phenylisopropylamines involves the synthesis of the corresponding phenylnitropropenes which are then reduced by lithium aluminum hydride. This route, as well as other methods used to prepare phenylisopropylamines, has been elaborated on in the literature survey.

Various attempts were made to synthesize aldehydes of general structure (74) which were the necessary precursors of the required nitropropenes. The first method attempted was the formylation of various 2-substituted-1,4-dimethoxybenzenes using phosphorous oxychloride and N-methylformanilide⁽¹²⁾. The dimethoxybenzene derivatives employed in this reaction (75c, 75d) were synthesized from the corresponding dihydroquinones (75a) and (75b) using dimethyl sulfate⁽¹⁴⁰⁾. These former compounds, because of the ortho and para directing properties of the ring substituents, were expected to formylate at the C-atom para to the substituent R¹. Using this synthetic method, the desired aldehydes (74a) and (74b) were isolated in very small yield, and the method was discontinued.

A second attempt to prepare the p-chloroaldehyde (74a) was by means of a Reimer-Tiemann reaction⁽¹⁴¹⁾ on

compound (75a). This was unsuccessful.

Because of the relatively high price of halogenated dihydroquinones, an alternative approach to the synthesis of the aforementioned aldehydes was sought. The usefulness of the Sandmeyer reaction⁽¹⁴²⁾ was then investigated. The precursor to the aldehydes (74a - 74c) employing this reaction is 4-amino-2,5-dimethoxybenzaldehyde (74e).

Because 2,5-dimethoxyaniline would be protonated under the formylation reaction conditions previously employed, thereby directing formylation to the position meta to the amino group, 2,5-dimethoxyacetanilide was prepared from commercially available 2,5-dimethoxyaniline, then subjected to the formylation reaction. Since the ring substituents are ortho and para directing to electrophilic reagents, formylation would be expected to occur para to the amide substituent and yield 4-acetamido-2,5-dimethoxybenzaldehyde (74f). Unfortunately 4-acetamido-2,5-dimethoxybenzaldehyde was not recovered after this reaction was completed. The high temperature resulting from the exothermic reaction, in addition to the large volumes of hydrogen chloride produced, provided conditions sufficient to hydrolyze the amide bond prior to ring formylation.

The preparation of 2,5-dimethoxy-4-nitrobenzaldehyde (74d) was then undertaken. Reduction of this material was expected to yield 4-amino-2,5-dimethoxybenzaldehyde. The synthesis of this compound (74d) was deemed possible by

the nitration of 2,5-dimethoxybenzyl alcohol followed by oxidation to the desired aldehyde (74d). The precursor, 2,5-dimethoxybenzyl alcohol, was isolated from the sodium borohydride reduction of commercially available 2,5-dimethoxybenzaldehyde. When a solution of 2,5-dimethoxybenzyl alcohol in acetic acid was treated with nitric acid⁽¹⁴³⁾, a mono-nitrated compound was isolated in good yield. The oxidation of the alcohol was accomplished in poor yield by passing air through a refluxing solution of the alcohol in dimethyl sulfoxide⁽¹⁴⁴⁾. The product recovered had a melting point identical with that reported for 2,5-dimethoxy-4-nitrobenzaldehyde⁽¹⁴⁵⁾. This synthetic approach was discontinued when the reduced product, 4-amino-2,5-dimethoxybenzaldehyde, was not recovered following catalytic hydrogenation of (74d).

Since the nitration of 2,5-dimethoxybenzyl alcohol yielded 2,5-dimethoxy-4-nitrobenzyl alcohol, it was reasoned that N-substituted 1-(2,5-dimethoxyphenyl)isopropylamines would nitrate similarly and yield the N-substituted 1-(2,5-dimethoxy-4-nitrophenyl)isopropylamine. Thus the nitration of N-acetyl-1-(2,5-dimethoxyphenyl)isopropylamine (77) was studied. This latter material was prepared by treating 2,5-dimethoxybenzaldehyde with nitroethane⁽⁴⁰⁾. The resulting nitropropene (76) was then reduced with lithium aluminum hydride to yield 1-(2,5-dimethoxyphenyl)isopropylamine (10f). Acetylation of (10f) with

acetic anhydride yielded N-acetyl-1-(2,5-dimethoxyphenyl)-isopropylamine (77).

When N-acetyl-1-(2,5-dimethoxyphenyl)isopropylamine was subjected to the same reaction conditions which led to the nitration of 2,5-dimethoxybenzyl alcohol at the 4-position, N-acetyl-1-(2,5-dimethoxy-4-nitrophenyl)isopropylamine (78) was formed and recovered in excellent yields. Verification that nitration had occurred at the 4-position was obtained from nmr spectral data. Since the coupling constant between aromatic protons para to each other is very small (0.4 cps)⁽¹⁴⁶⁾, the two aromatic protons of N-acetyl-1-(2,5-dimethoxy-4-nitrophenyl)isopropylamine, which are para to each other, should appear as broadened singlets. The nmr spectrum of this material did, in fact, show the presence of two singlets in the aromatic region. Alternatively, if nitration had occurred at the 3-position, the protons would be meta to each other and two doublets should have been evident because of the larger meta coupling constant (1.8 cps).

Unlike 2,5-dimethoxy-4-nitrobenzaldehyde, N-acetyl-1-(2,5-dimethoxy-4-nitrophenyl)isopropylamine when subjected to catalytic hydrogenation readily incorporated hydrogen and an excellent yield of N-acetyl-1-(4-amino-2,5-dimethoxyphenyl)isopropylamine hydrochloride (79) was recovered.

N-Acetyl-1-(4-chloro-2,5-dimethoxyphenyl)isopropylamine (80a) and N-acetyl-1-(4-iodo-2,5-dimethoxyphenyl)iso-

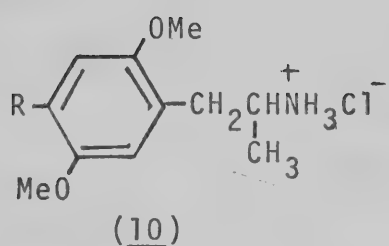
propylamine (80c) were then successfully prepared by subjecting N-acetyl-1-(4-amino-2,5-dimethoxyphenyl)isopropylamine to the Sandmeyer reaction⁽¹⁴²⁾, and N-acetyl-1-(4-bromo-2,5-dimethoxyphenyl)isopropylamine (80b) was obtained by treating N-acetyl-1-(2,5-dimethoxyphenyl)isopropylamine with bromine-water.

A suitable means of hydrolyzing the amide group of compounds (78, 79 and 80a - 80c), thereby completing the last step in the synthetic route summarized by Scheme 6, was investigated. These aliphatic amides proved to be resistant to hydrolysis by either hydrochloric acid or aqueous sodium hydroxide. In those instances when hydrolysis was successful, the amines were obtained in low yields. A procedure employing ethylene glycol and sodium hydroxide was used eventually⁽¹⁴⁷⁾. This reagent successfully hydrolyzed each of the acetylated analogs (80a - 80c) and reasonable yields of the amines (10e), (10g) and (10h) were recovered.

1-(2,5-Dimethoxy-4-nitrophenyl)isopropylamine (10i) was similarly prepared by the hydrolysis of N-acetyl-1-(2,5-dimethoxy-4-nitrophenyl)isopropylamine (78).

Although the hydrolysis of N-acetyl-1-(4-amino-2,5-dimethoxyphenyl)isopropylamine (79) was successful, the product, 1-(4-amino-2,5-dimethoxyphenyl)isopropylamine (10j), was difficult to purify by crystallization. An alternative procedure, in which 1-(2,5-dimethoxy-4-nitrophenyl)isopro-

pylamine was catalytically reduced, provided the pure derivative (10j).



R = Me (10c)

R = Et (10d)

R = Br (10e)

R = H (10f)

R = Cl (10g)

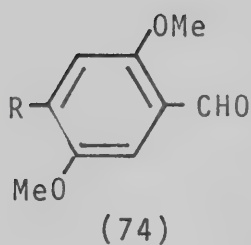
R = I (10h)

R = NO₂ (10i)

R = NH₂ (10j)

R = NHCOCH₃ (10k)

R = NHCHO (10l)



R = Cl (74a)

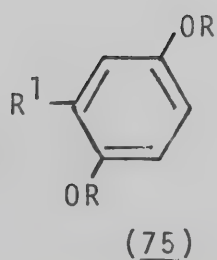
R = Br (74b)

R = I (74c)

R = NO₂ (74d)

R = NH₂ (74e)

R = NHCOCH₃ (74f)

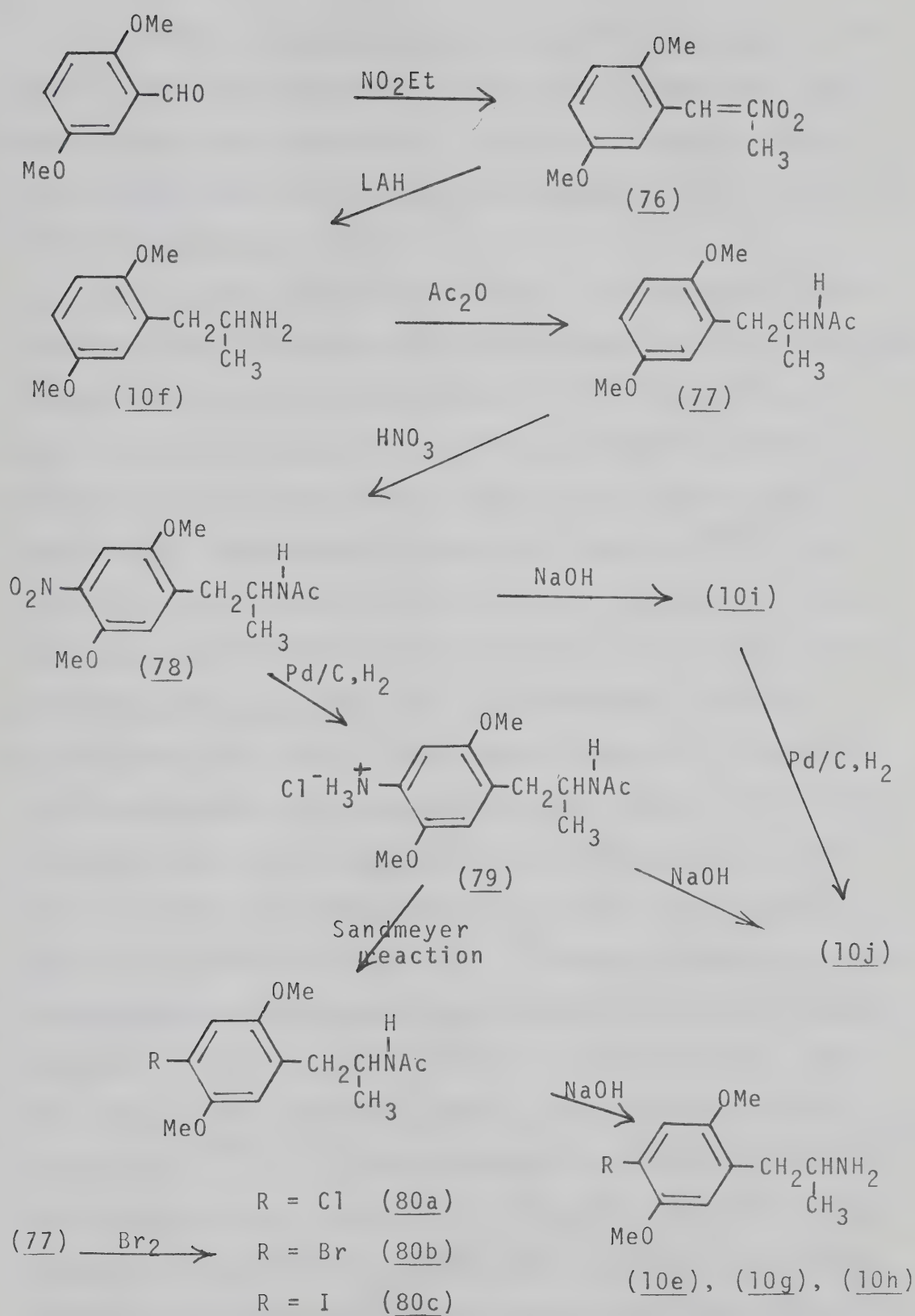


R = H; R¹ = Cl (75a)

R = H; R¹ = Br (75b)

R = Me; R¹ = Cl (75c)

R = Me; R¹ = Br (75d)



Scheme 16

As will be elaborated on in another section of this thesis, with the exception of the 4-amino compound (10j), each of the other analogs R = Cl, Br, I, and NO₂ (10g), (10e), (10h), and (10i), were pharmacologically active when they were tested on rats.

A possible explanation of why 1-(4-amino-2,5-dimethoxyphenyl)isopropylamine failed to demonstrate any pharmacological activity may be the result of its inability to reach the site of its action. For psychoactive drugs to display their activity, they must first traverse the highly lipid theoretical blood-brain barrier⁽¹⁴⁸⁾. At physiological pH both basic centers of 1-(4-amino-2,5-dimethoxyphenyl)isopropylamine would be protonated, thereby retarding passage across the lipid membrane. Hence, it was rationalized that if the 4-amino group of 1-(4-amino-2,5-dimethoxyphenyl)isopropylamine was acetylated to form 1-(4-acetamido-2,5-dimethoxyphenyl)isopropylamine (10k), which has only one basic center, it might then be able to cross the blood-brain barrier. O⁶-Monoacetylmorphine (MAM) the principal intermediate metabolite of heroin is thought to readily enter the brain⁽¹⁴⁹⁾. It is believed, then, that once inside the brain, MAM is then converted back to morphine⁽¹⁴⁹⁾. If 1-(4-acetamido-2,5-dimethoxyphenyl)isopropylamine does enter the brain, then the ubiquitous acetylase enzyme might, as with MAM, hydrolyze the amide to form 1-(4-amino-2,5-dimethoxyphenyl)isopropylamine.

Therefore the preparation of 1-(4-acetamido-2,5-dimethoxyphenyl)isopropylamine was undertaken. The synthetic route summarized by Scheme 16 cannot be utilized for the synthesis of this compound. If this route were employed, hydrolysis of the precursor, N-acetyl-1-(4-acetamido-2,5-dimethoxyphenyl)isopropylamine would, from previously described data, result in the formation of N-acetyl-1-(4-amino-2,5-dimethoxyphenyl)isopropylamine (79).

The most obvious alternative synthetic route involved the preparation of the oxime of N-acetyl-2,5-dimethoxyphenylacetone (86) which would be expected to reduce catalytically to the desired amine (10k)⁽¹⁵⁰⁾. This series of reactions is shown in Scheme 17.

The starting material for these reactions, namely 2,5-dimethoxyphenylacetone (81), was one of the products recovered following the catalytic reduction of 1-(2,5-dimethoxyphenyl)-2-nitropropene-1. Also isolated from the reaction mixture was the oxime of 2,5-dimethoxyphenylacetone (82). Both of these compounds were characterized by means of elemental analysis as well as infrared and mass spectral data.

Utilizing the previously described reaction conditions 2,5-dimethoxyphenylacetone was nitrated to form 2,5-dimethoxy-4-nitrophenylacetone (83). The position at which nitration occurred was confirmed by nmr spectral data as described earlier. Catalytic reduction of 2,5-dimethoxy-4-

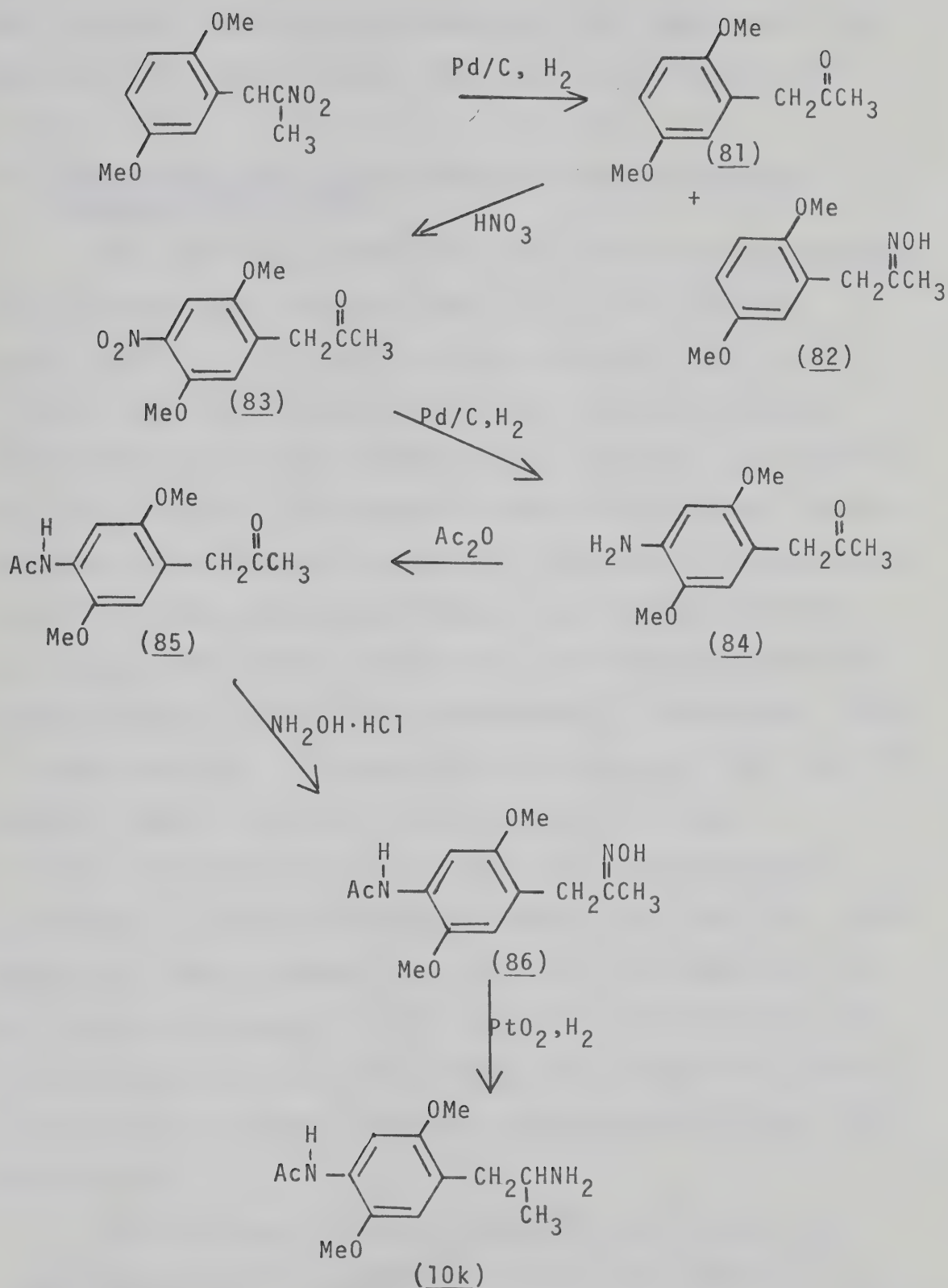
nitrophenylacetone yielded 4-amino-2,5-dimethoxyphenylacetone (84). The acetylated derivative (85) was prepared by treating 4-amino-2,5-dimethoxyphenylacetone with acetic anhydride. Preparation of the oxime (86), although somewhat difficult, was successful. Catalytic hydrogenation of this material yielded the desired amine (10k).

Each of the above products was characterized by infrared and nmr spectral data as well as elemental analysis determinations.

After intraperitoneal injection of 1-(4-acetamido-2,5-dimethoxyphenyl)isopropylamine hydrochloride into a rat, no obvious symptoms characteristic of DOM intoxication were observed. The apparent inactivity of this compound in rats may be the result of several factors.

The compound may have been hydrolyzed rapidly to 1-(4-amino-2,5-dimethoxyphenyl)isopropylamine which would not be expected to enter the brain to any extent. Alternatively, 1-(4-acetamido-2,5-dimethoxyphenyl)isopropylamine might be inactive for two reasons, even if it did gain entry to the brain. An esterase enzyme might not be present to convert it to the amino-compound, and if the acetamido group persisted, its size might be detrimental to attachment of the compound at the receptor site.

If the absence of activity is the result of steric rather than electronic influences, then a pharmacological study of 1-(2,5-dimethoxy-4-formamidophenyl)isopropylamine



Scheme 17

may indicate how sterically important this portion of the molecule is. Such a study, however, was not undertaken.

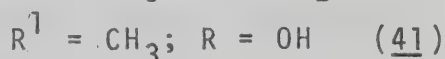
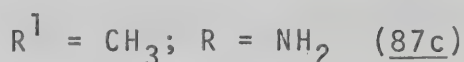
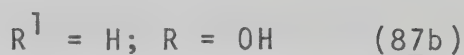
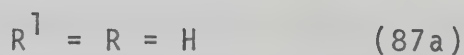
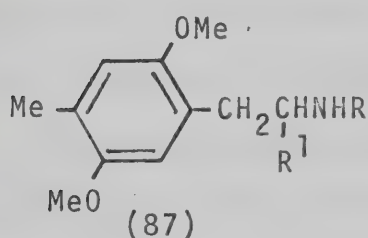
b) Some Analogs of 1-(2,5-Dimethoxy-4-methylphenyl)-isopropylamine (DOM)

The majority of reported structure-activity relationship studies have involved modifications of the ring substituents in the phenethylamine molecule. Only a few studies have been undertaken on the effects of changing other portions of the phenethylamine molecule. The purpose of this portion of the present study was to prepare analogs of DOM with different basicities. Subsequent testing would determine what effect such changes have on psychotomimetic activity. This study could assist in determining whether phenethylamines, LSD, and psychotomimetic tryptamines share a common receptor. Current theories postulate that they do share a common receptor. If Kang's theory (page 24) is correct, then maximal activity for the psychotomimetic tryptamines and phenethylamines should occur when the amino groups of these compounds are tertiary. Although this is so for the tryptamines⁽¹⁵¹⁾, a study⁽¹⁸⁾ of secondary and tertiary derivatives of DOM showed these were less active psychotomimetic agents than the corresponding primary amino derivatives.

The decrease in psychotomimetic activity of the phenethylamines on formation of the tertiary derivative would suggest that the psychotomimetic phenethylamine drugs

do not interact with the same receptor or in the same fashion as LSD, as described by Kang. However, the differences in activity of the primary, secondary, and tertiary phenethylamines may be the result of different concentrations of the drug reaching the site of action.

All the compounds investigated (87a - 87c) are analogs of DOM. This parent structure was chosen because it is a very potent psychotomimetic drug. It was felt that even if the envisaged derivatives were considerably less active than DOM, possible psychoactive properties might still be detectable.



Compound (87a) has been prepared and reported⁽¹⁸⁾ to have psychotomimetic properties. The nitrogen atom of the amino group in derivatives (87b) and (87c) is less basic than the nitrogen atom of DOM. Therefore, if the postulate of Kang is correct, the affinity of these derivatives toward the receptor should be less and a decrease in psychotomimetic activity should result.

2,5-Dimethoxy-4-methylphenethylamine was obtained as outlined in Scheme 18. The necessary aldehyde for this

reaction, namely 2,5-dimethoxy-4-methylbenzaldehyde (88), was synthesized by formylation of 2,5-dimethoxytoluene employing N-methylformanilide and phosphorus oxychloride⁽¹²⁾. A good yield of product was isolated. Only one isomer was isolated in which the formyl group entered the benzene ring para to the methyl group as evidenced by the presence of two singlets in the aromatic region of the nmr spectrum. The appearance of two similar signals was observed previously with similarly substituted phenylisopropylamines.

2,5-Dimethoxy-4-methyl- β -nitrostyrene (89b) was prepared by first treating a methanolic solution of 2,5-dimethoxy-4-methylbenzaldehyde and nitromethane with a solution of sodium hydroxide and then adding the sodium salt of the condensation product (89a) to hydrochloric acid⁽¹⁵²⁾.

An ether solution of (89b) was reduced to 2,5-dimethoxy-4-methylphenethylamine (87a) with lithium aluminum hydride⁽¹⁷⁾.

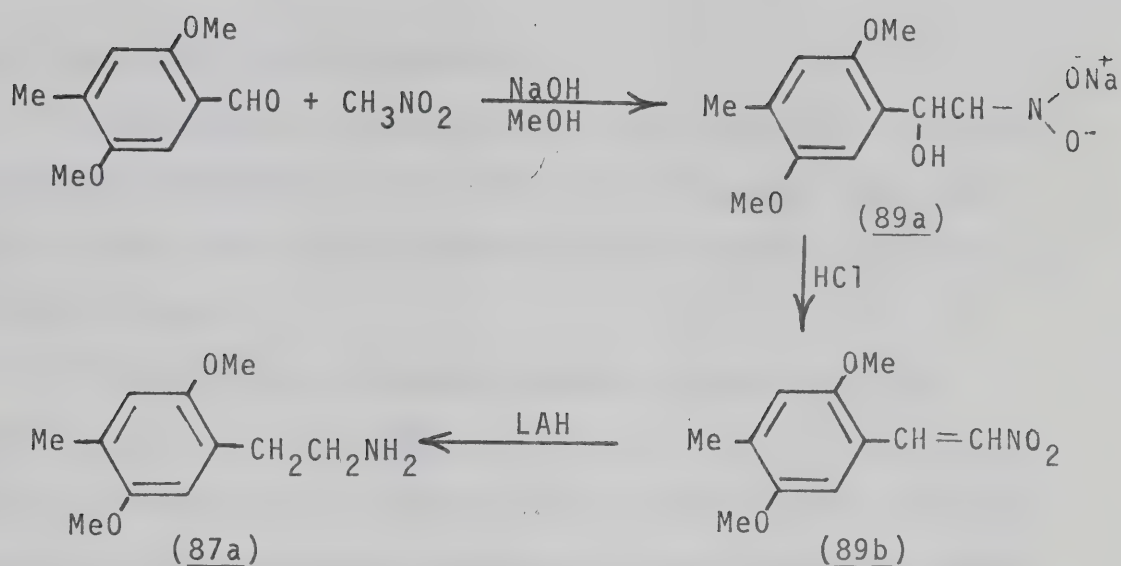
Hydroxylamine compounds have been prepared by several methods including the reduction of the corresponding nitropropenes by the inverse addition of lithium aluminum hydride at very low temperatures⁽⁵⁹⁾, by hydrogenating the corresponding oxime in the presence of a catalyst⁽⁵⁹⁾, and by reduction of the corresponding nitroalkane with zinc and ammonium chloride⁽¹⁵³⁾. The latter method was employed to prepare N-(2,5-dimethoxy-4-methylphenethyl)hydroxylamine.

The necessary precursor, 1-(2,5-dimethoxy-4-methyl-

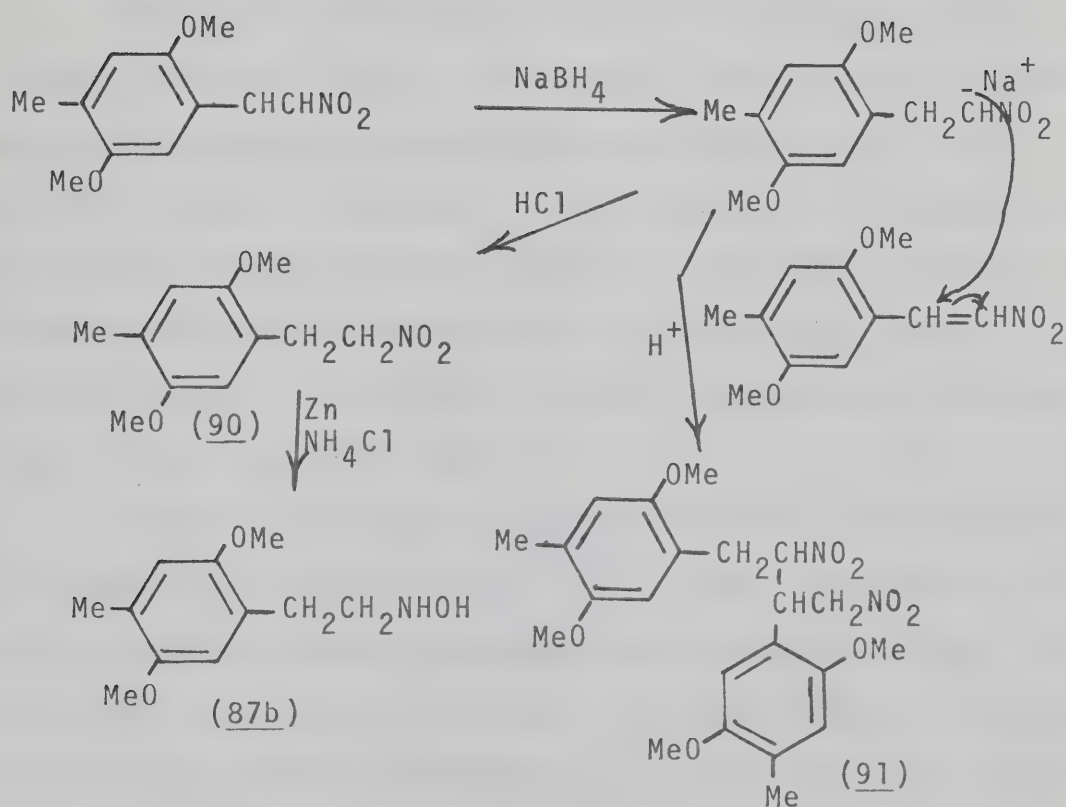
phenyl)-2-nitroethane (90) was obtained when 2,5-dimethoxy-4-methyl- β -nitrostyrene was reduced with sodium borohydride. The crude reaction mixture from the reduction was found to consist of at least two compounds which were easily separated because of differences in their solubilities in ethanol. One compound had an elemental analysis and an nmr spectrum agreeing with structure (90). Present in this latter spectrum were signals which could be ascribed to two aromatic protons. Also present were three 3-proton singlets (i.e. the 4-methyl and 2- and 5-methoxy groups) and two 2-proton methylene doublets which were coupled to each other. The nmr spectrum of the other material was complex.

Shechter et al. ⁽¹⁵⁴⁾ found that the sodium borohydride reduction of nitroolefins was accompanied by a concurrent reaction of the Michael-type in which the primary reduction product, the salt of the nitroalkane, added to the initial nitroolefin to yield a salt of a 1,3-nitroalkane. Therefore the other product from the reduction of 2,5-dimethoxy-4-methyl- β -nitrostyrene was thought to be that shown by structure (91). It could have formed as shown in Scheme 19.

The molecular ion in the mass spectrum of the ethanol-insoluble compound was present at m/e 448, which corresponds to the molecular weight of the dinitroalkane (91). The elemental analysis of this compound was



Scheme 18



Scheme 19

consistent with this structure.

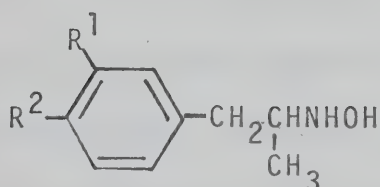
An ethanolic solution of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitroethane was heated with zinc and ammonium chloride to yield N-(2,5-dimethoxy-4-methylphenethyl)hydroxylamine (87b).

A preliminary pharmacological screening of the hydrochloride salt of (87b) in rats at the relatively high dose of 60 mg/kg (ip) showed that it had effects such as pupillary dilatation and hypersalivation similar to those caused by DOM. The rat was also observed to walk backwards following a circular path.

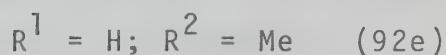
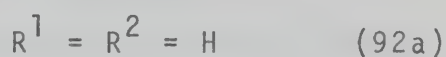
Because of the apparent positive psychopharmacological effect of (87b), the higher homolog, N-(2,5-dimethoxy- α ,4-dimethylphenethyl)hydroxylamine (41), might also be an active compound. This compound was isolated as one of the products of the reduction of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene-1 (see page 98), but a pharmacological evaluation of this compound was not undertaken in the present study.

Compounds similar to (87b) have been prepared and evaluated by Benington *et al.*⁽¹⁵⁰⁾. They prepared the ring substituted N-(α -methylphenethyl)hydroxylamines (92a - 92e) and found a decrease in central stimulant effects relative to the corresponding amphetamine. As was found for phenethylamines⁽¹⁵⁵⁾, introduction of a methoxy, chloro, or methyl group into the 4-position of the benzene ring

intensified the CNS stimulant effects of the aralkylhydroxylamine. The onset of action was short and, excluding (92e), decreased hexobarbital sleeping time. Except for (92c), these compounds produced a rage response and increased rectal temperatures in cats. Similar effects had been observed with the corresponding amphetamines.



(92)

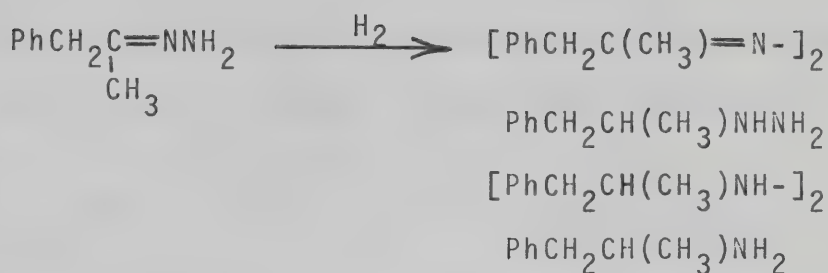


The synthesis of N-(2,5-dimethoxy- α ,4-dimethylphenethyl)hydrazine (87c) was next undertaken. The most common methods reported in the literature to prepare 1-(α -methylphenethyl)hydrazines involve reaction of the corresponding 1-phenyl-2-bromo(chloro)propane with hydrazine⁽¹⁵⁶⁻¹⁵⁸⁾, or the reduction of the hydrazone formed by the interaction of the corresponding phenylacetone with hydrazine^(157,160,161). Numerous examples of 1-(α -methylphenethyl)hydrazines are present in the literature and possess a wide range of activities including monoamine oxidase inhibiting properties⁽¹⁵⁶⁻¹⁶²⁾, analgesic and antipyretic^(163,164), central stimulating⁽¹⁵⁷⁾, antidepressant⁽¹⁶⁵⁾, and diuretic properties⁽¹⁶⁰⁾. Thus the

interesting hybrid (87c) could possess other pharmacological activities in addition to possible psychotomimetic properties.

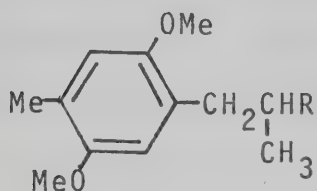
Although the simple reaction of 2,5-dimethoxy-4-methylphenylacetone with hydrazine followed by reduction would be expected to provide the desired structure (87c), this was not found to be the case. After a methanolic solution of the hydrazine and 2,5-dimethoxy-4-methylphenylacetone was heated under reflux for one hour, the solvent was evaporated, leaving a light brown oil. The infrared spectrum lacked a carbonyl absorption band and suggested that hydrazone formation had occurred. An attempt to isolate the hydrazone by formation of the hydrochloride salt was unsuccessful. A solution of the crude material in methanol and acetic acid was then hydrogenated at 50 psi in the presence of platinum dioxide. A basic component was isolated and found to be DOM. The residue remaining after the removal of DOM was an oil. Its infrared spectrum displayed a carbonyl absorption band near 1710 cm^{-1} . The oil also gave a red precipitate when treated with 2,4-dinitrophenylhydrazine. It obviously contained a ketonic product, probably starting phenylacetone.

Beil et al.⁽¹⁵⁹⁾ encountered some synthetic difficulties when studying the reduction of 1-(α -methylphenethyl) hydrazone. The products they isolated are summarized in the following chart.



The mass spectrum of the oil isolated in the present study showed it consisted of several components. A peak was present at m/e 208 which corresponded to 2,5-dimethoxy-4-methylphenylacetone. Although only in very low abundance, peaks were present at m/e 228 and 230 in the approximate ratio of three to one, which is indicative of the presence of a covalently bonded chlorine. This corresponds to a chlorinated 1-(2,5-dimethoxy-4-methylphenyl)propane. The immediate loss of a chlorine-containing fragment from the m/e 228, 230 molecular ion would suggest that the chlorine atom was not bonded to the benzene ring. Structure (93b) would fit the mass spectral evidence. The origin of such a compound, however, is not obvious. Its formation could have arisen during the work-up procedure of the reaction. This is probable since, if it existed prior to the reduction reaction it would have reduced to form 1-(2,5-dimethoxy-4-methylphenyl)propane (93c). If 1-(2,5-dimethoxy-4-methylphenyl)-2-propanol (93a) was present during the work-up procedure, then it could be a precursor to (93b). The molecular weight of this alcohol (93a) is 210. Such a mass was present in the mass spectrum. The presence of an ion

at m/e 194 indicated that 1-(2,5-dimethoxy-4-methylphenyl)-propane might also be present in the crude mixture.



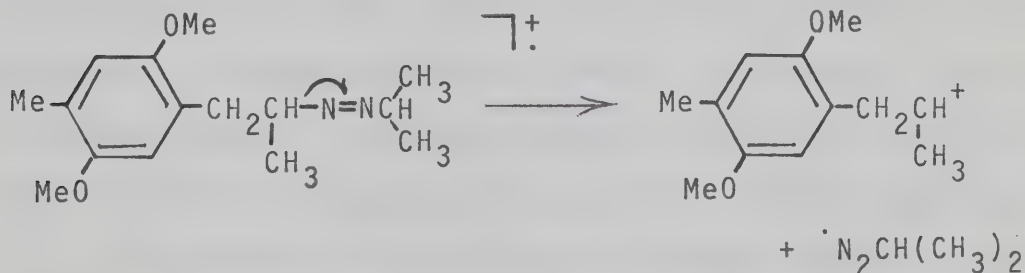
(93)

R = OH (93a)

R = Cl (93b)

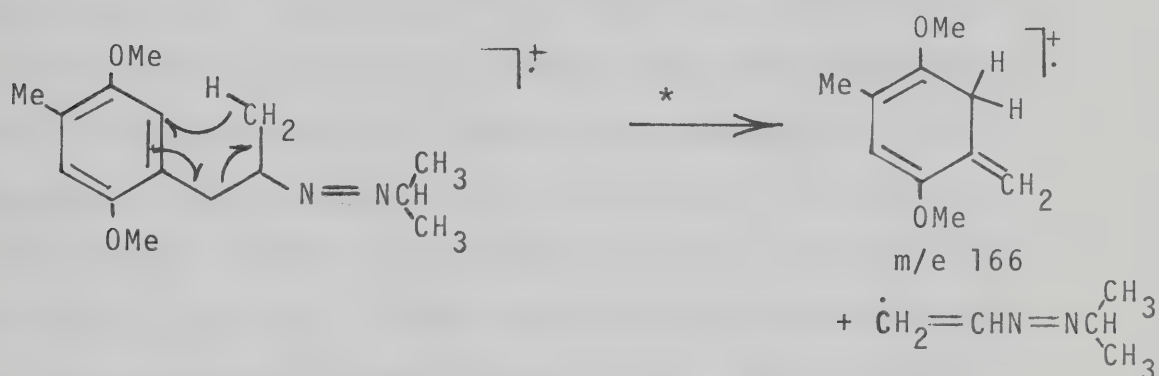
R = H (93c)

When the reaction was repeated, a water-soluble, solid material was recovered following the hydrogenation. The infrared spectrum of this solid displayed bands characteristic of a tertiary amine salt. Examination of the mass spectrum of this compound revealed the presence of the molecular ion located at m/e 264; no other significant ions were present until m/e 193. This latter weight corresponds to the formula $C_{12}H_{17}O_2$. The appearance of an infrared absorption band near 1650 cm^{-1} suggested the presence of an azo-group; thus structure (94) is a possibility.



(94)

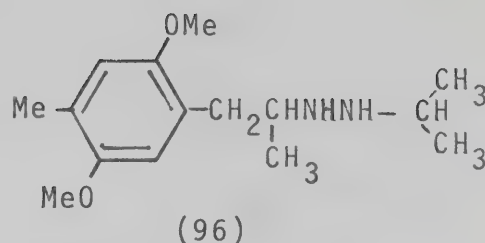
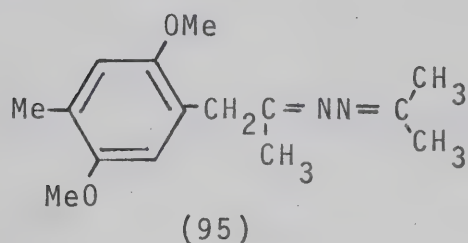
An ion of much greater abundance was present at m/e 166. Assuming structure (94) to be correct, then this fragment could arise through a reverse Diels Alder reaction as shown below. A metastable ion was present at m/e 104.4 further indicating that (94) fragmented directly to the m/e 166 fragment.



The elemental analysis and nmr spectrum of the compound were in agreement with structure (94). Present in the spectrum was a broad 2-proton aromatic signal, a 6-proton singlet (two overlapping 3-proton methyl ether signals), a 6-proton doublet (two methyl groups), and a 3-proton singlet (4-methyl group) as well as a 4-proton broad multiplet (two methylene and two methine protons).

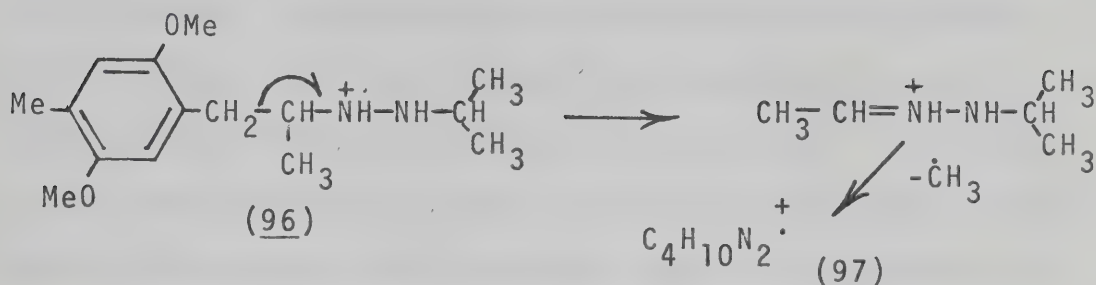
The origin of (94) is not obvious though a possible explanation is that somehow the apparatus was contaminated with acetone at some stage in the reaction sequence with subsequent formation of the intermediate (95) which reduced

to the product (94).

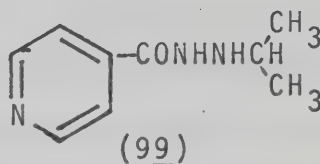
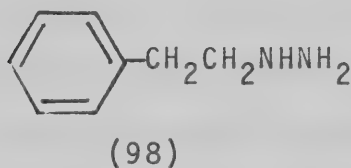


Because of the lack of starting material, experiments to clarify the origin of this compound were not undertaken. When it was subjected to further hydrogenation in the presence of platinum dioxide at 50 psi for 12 hours, a product which melted at a temperature very close to that of DOM was isolated. Mixed melting point determinations of these compounds showed a depression. The infrared spectrum of this material did not display tertiary amine salt absorption bands. However, present in the spectrum were what appeared to be peaks characteristic of a primary or a secondary amine salt. The molecular ion in the mass spectrum of this compound was present at m/e 266; this corresponds to the molecular weight of the hydrazine (96). In addition, fragment ions at m/e 193 and 166 were present and the base peak was located at m/e 86. This latter ion could be that shown by structure (97). A possible mechanism for its formation is shown on the following page. Structure (96) is an interesting compound since it bears a structural resemblance to the three psychoactive compounds DOM, phenelzine (98) and iproniazid (99). These latter two drugs

are monoamine oxidase inhibitors.



Further investigation of the preparation of N-(2,5-dimethoxy- α ,4-dimethylphenethyl)hydrazine was not undertaken because of the difficulties encountered in the synthesis just described.



c) Preparation and Properties of Some α -Carboxyphenethylamines (Phenylalanines)

When mescaline is administered to animals, the amount which reaches the brain is very low^(74,75). In an attempt to obtain higher brain levels, the amino acid analog, 3,4,5-trimethoxyphenylalanine, was prepared and tested^(81,82). It was rationalized that this compound would be actively transported across the blood-brain barrier and be decarboxylated to yield mescaline. This compound when tested, however, failed to demonstrate any psychotomimetic activity.

It appears likely that decarboxylation of the amino acid did not occur. Structure-activity studies of psychotomimetic drugs show that maximal hallucinogenic activity is achieved when there is a methyl branch at the α -position on the ethylamine side chain. Increasing the chain length beyond the optimal three carbons results in a decrease in psychotomimetic activity. The carboxylic acid group at the α -position in mescaline thereby forming the amino acid (34) would be analogous to increasing the chain length of the phenylisopropylamine psychotomimetic drugs beyond the optimum three carbon chain.

Apparently no one has attempted to explain why increasing the side chain length of the psychotomimetic phenylisopropylamines beyond three carbons results in a decrease in activity. A possible explanation may be that larger groups at the α -position sterically interfere with the amino group interacting with the receptor.

It may be possible to gain some knowledge of how detrimental the carboxylic acid group is to psychotomimetic activity by preparing and testing the corresponding amino acid analogs of potent psychotomimetic drugs such as 1-(2,5-dimethoxyphenyl)isopropylamine, 1-(2,5-dimethoxy-4-methylphenyl)isopropylamine (DOM), or 1-(4-bromo-2,5-dimethoxyphenyl)isopropylamine. None of these compounds would be expected to act as substrates for brain decarboxylase enzymes⁽⁸³⁾; therefore they should exist unchanged in

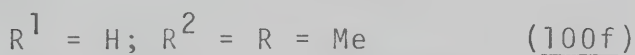
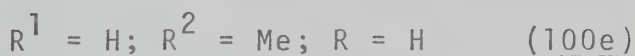
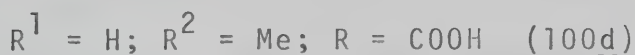
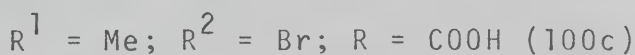
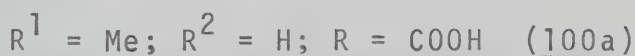
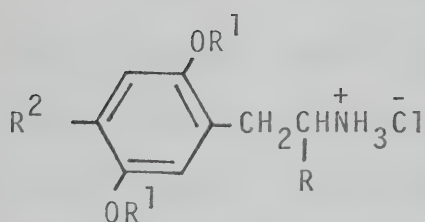
the brain. Even if the activity of these amino acid analogs was 80 times less than the corresponding phenethylamines, they would at least be as potent as mescaline and hence their activities would be detectable.

These compounds are interesting for other reasons. Since they are amino acids, they would be expected to easily enter the CNS, and because they closely resemble psychotomimetic agents, they may induce other psychopharmacological actions in addition to possible psychotomimetic effects. A psychedelic experience consists of many component effects. For instance, some psychotomimetics induce visual changes and time alterations, etc. It is therefore not unrealistic to consider that compounds such as these amino acids might have predominantly one of these component activities. It appears that the amino acid analog of mescaline has only been tested on rats, and hence such an activity may have been undetected.

For the reasons cited, and since 3,4,5-trimethoxyphenylalanine is the only example of an amino acid patterned after a known hallucinogen and evaluated for psychotomimetic activity, preparations of 2,5-dimethoxy-4-methylphenylalanine (100b), 2,5-dimethoxyphenylalanine (100a), and 4-bromo-2,5-dimethoxyphenylalanine (100c) were undertaken.

In view of the study of Ferrini and Glasser, it was thought that 2,5-dihydroxy-4-methylphenylalanine (100d) might be decarboxylated by the brain decarboxylase enzyme.

Since it is an amino acid, it would presumably be actively transported into the brain and subsequent decarboxylation within the brain would provide 2,5-dihydroxy-4-methylphenethylamine (100e). This compound is not unlike 2,5-dimethoxy-4-methylphenethylamine (87a) which has been found to possess hallucinogenic properties⁽¹⁸⁾. Therefore the possibility of 2,5-dihydroxy-4-methylphenylalanine possessing psychotomimetic activity once inside the central nervous system is interesting. Neither 2,5-dihydroxy-4-methylphenethylamine (100e) nor 1-(2,5-dihydroxy-4-methylphenyl)isopropylamine (100f), like adrenaline and serotonin (32a), would pass the blood brain barrier because of the polar nature of the hydroxyl groups⁽¹⁶⁶⁾. Therefore they would not be expected to possess central activity.



Two interesting questions arise: are the methoxy groups on DOM necessary for activity at the receptor or, in addition to supplying the benzene ring with electrons in order for it to interact with the receptor⁽²⁸⁾, are they

necessary to assist the passage of the otherwise inactive compound⁽¹⁶⁶⁾ across the blood-brain barrier? Would the hydroxyl groups of 2,5-dihydroxy-4-methylphenylalanine provide the same function as the methoxy groups of DOM once inside the central nervous system at the receptor site? In an attempt to answer these questions and to gain an insight into the functions of the ether groups of DOM, the preparation of 2,5-dihydroxy-4-methylphenylalanine was undertaken to compare its pharmacological activity with that of 2,5-dimethoxy-4-methylphenethylamine.

Phenylalanines have been prepared by a variety of methods including the Erlenmeyer azlactone reaction⁽¹⁶⁷⁾ which was investigated as a possible route for the preparation of 2,5-dimethoxy-4-methylphenylalanine. This synthetic route is summarized by Scheme 20.

When 2,5-dimethoxy-4-methylbenzaldehyde reacted with acetylglycine, acetic anhydride and sodium acetate, the bright orange azlactone of α -acetylamino-2,5-dimethoxy-4-methylcinnamic acid (103b) was formed. This crude azlactone was then hydrolyzed with water to yield α -acetamino-2,5-dimethoxy-4-methylcinnamic acid (104b). N-Acetyl-2,5-dimethoxy-4-methylphenylalanine (105b) was isolated in good yield after α -acetamido-2,5-dimethoxy-4-methylcinnamic acid was hydrogenated in the presence of palladium-charcoal. This latter material (105b) was then treated with hydrochloric acid; this resulted in the hydrolysis of the amide

with the subsequent formation of 2,5-dimethoxy-4-methyl-phenylalanine hydrochloride (100b).

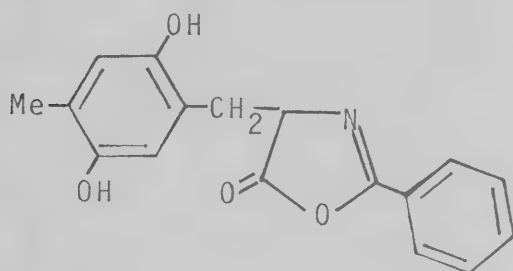
The same sequence of reactions was used, starting with 2,5-dimethoxybenzaldehyde (101). The intermediates (103a), (104a) and (105a), as well as the final product (100a), were isolated and characterized.

The synthesis of (105c) was accomplished by treating N-acetyl-2,5-dimethoxyphenylalanine (105a) with bromine-water. Bromination occurred at the 4-position as was evident from the appearance of two singlets in the aromatic region of the nmr spectrum. The amide was then hydrolyzed with hydrochloric acid to yield 4-bromo-2,5-dimethoxyphenylalanine hydrochloride (100c).

The first method tried to prepare (100e) was attempted cleavage of the ether groups of the dimethoxy analog (100b) with hydriodic acid⁽¹⁶⁸⁾. However, on completion of the reaction, only a dark oil was recovered. After attempts to isolate a pure compound from the oil failed, an alternate synthesis was investigated.

A reported⁽¹⁶⁹⁾ successful preparation of phenylalanines was the treatment of the azlactone (103c) with red phosphorus and hydriodic acid. After a mixture of (103c), phosphorus, hydriodic acid, and acetic anhydride was heated under reflux for three hours, the phosphorus was removed by filtration, and the solvent was evaporated under reduced pressure. Water and ether were then added to the dark, oily

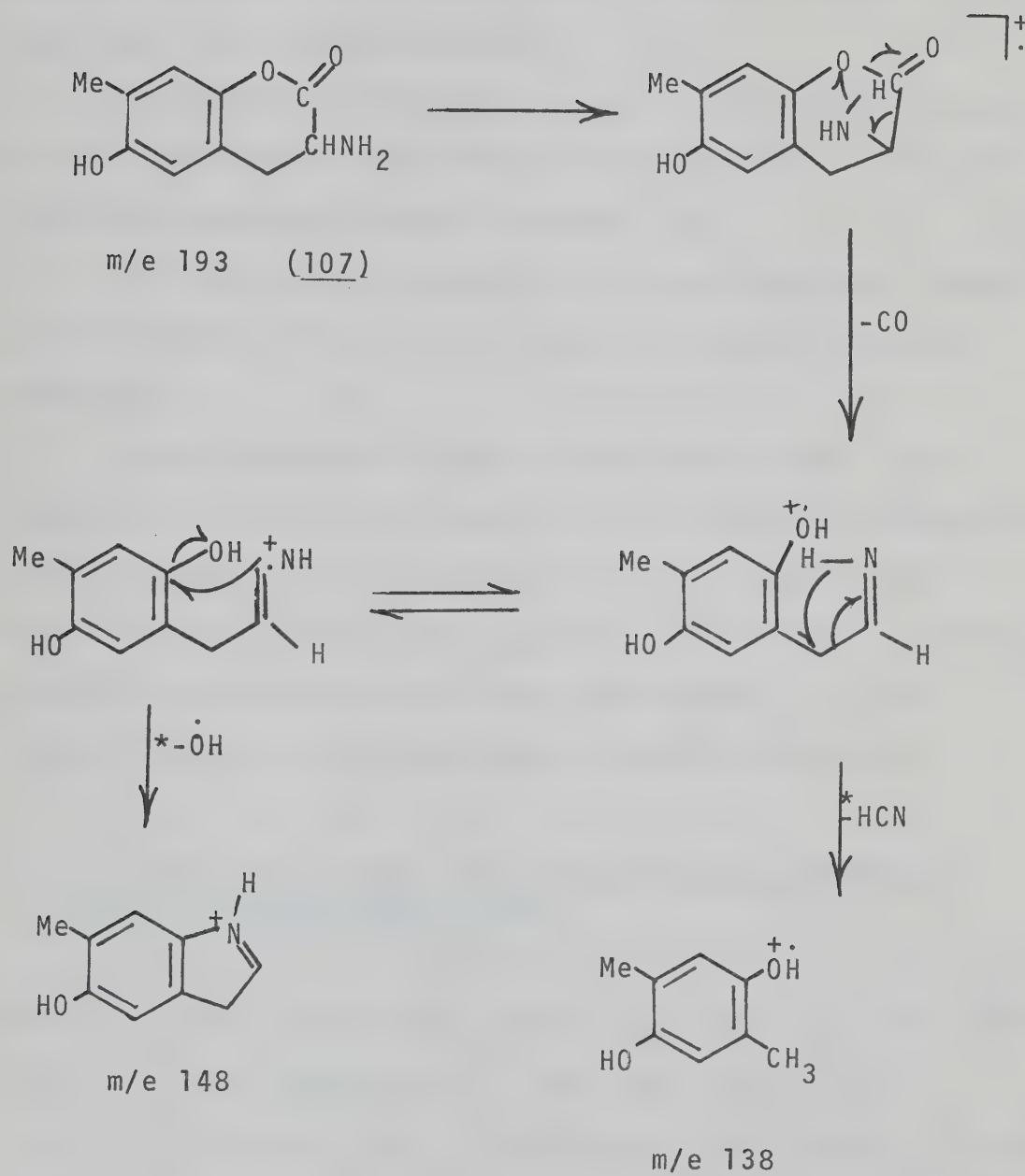
residue. A white solid was observed to form at the interface and was collected by filtration. The infrared spectrum of this material displayed bands at 1765 cm^{-1} (lactone), 1642 cm^{-1} ($\text{C}=\text{N}$), a sharp band at 3440 cm^{-1} , and a broad band at 3300 cm^{-1} (free and bonded OH). The molecular ion in the mass spectrum appeared at m/e 297. The above spectral data are in agreement with structure (106). Its elemental analysis also was consistent with (106).



(106)

The aqueous solution remaining after the removal of (106) formed a blue color when it was treated with ninhydrin reagent, indicating the presence of an α -amino acid⁽¹⁷⁰⁾. After several unsuccessful attempts to find the isoelectric points of the amino acid the solution was not further investigated.

The original reaction was repeated with the exception that the reflux time was extended to five hours. When the solvent was removed, a dark oil remained. The pH of an aqueous solution of the oil was adjusted to 4-5 with ammonium hydroxide and a solid precipitated from solution.



Scheme 21

3-proton methyl singlet, a 2-proton methylene doublet ($J=10$ cps), a 1-proton methine triplet, ($J=10$ cps), two 1-proton aromatic signals, and a very broad 2-proton signal which exchanged with deuterium oxide.

The elemental analysis, however, did not correspond to this structure. The analysis did, however, correspond to a mono-hydrated form of compound (107).

In view of this undesired lactone formation further investigations of methods of preparing (100e) were not undertaken.

Since structure (107) is relatively polar, and because it would not be expected to be actively transported into the brain, it would probably not be central acting. A preliminary screening of (107) in a rat showed it lacked symptoms characteristic of DOM intoxication. It did, however, appear to possess some stimulant properties.

d) Possible Metabolites of 1-(2,5-Dimethoxy-4-methyl-phenyl)isopropylamine (DOM)

The biological detoxification of both the psychotomimetic phenethylamine derivative, mescaline (2), and phenylisopropylamine (amphetamine), has been the subject of numerous investigations. A summary of the findings of these studies has been presented in the literature survey. When the present study was undertaken, metabolic studies on any of the methoxylated phenylisopropylamine psychotomimetic

drugs had not been reported. Therefore the preparation of some possible metabolites of a member of this class of compounds was undertaken. It was not the intention of the study to isolate and identify the metabolites of the drug from a biological system, but rather on the basis of the known routes of detoxification of mescaline and phenylisopropylamine, to prepare possible metabolites to be pharmacologically evaluated for hallucinogenic properties. Since DOM is the most potent of the methoxylated phenylisopropylamine hallucinogens, it was rationalized that if any metabolite of these psychotomimetic amines was active, it would be a metabolite of DOM. Therefore DOM was chosen as the parent compound for this study.

Friedhoff⁽⁹²⁾, after investigating mescaline and its metabolites, concluded that mescaline is a pro-drug and the metabolite 2-(3,4,5-trimethoxyphenyl)ethanol was responsible for the psychotomimetic activity attributed to mescaline.

In view of the known routes of detoxification of mescaline and amphetamine, it seemed reasonable to assume that structures (39), (41), (42), (93a), (108a) and (108b) could be intermediates in the metabolism of DOM. Two of these possible metabolites were considered as possible psychotomimetic agents, these being 1-(2,5-dimethoxy-4-methylphenyl)-2-propanol (93a) because of the study by Friedhoff et al.⁽⁹²⁾, and N-(2,5-dimethoxy- α ,4-dimethylphenethyl)hydroxylamine (41) because of its similarity to

DOM.

Although 2,5-dimethoxy-4-methylphenylacetic acid (108a) would not be expected⁽⁹⁵⁾ to be an active psychotomimetic agent, it is a useful intermediate in the synthesis of 2,5-dimethoxy-4-methylphenylacetone (108b). The synthesis of 2,5-dimethoxy-4-methylphenylacetic acid was undertaken employing a procedure described by Snyder *et al.*⁽¹⁷²⁾ for the preparation of 3,4-dimethoxyphenylacetic acid. In this procedure, a solution of the azlactone of α -benzoylamino-2,5-dimethoxy-4-methylcinnamic acid (103c) was hydrolyzed in sodium hydroxide solution, then oxidized with hydrogen peroxide to yield a mixture of 2,5-dimethoxy-4-methylphenylacetic acid (108a) and benzoic acid. These acids were separated by forming the respective methyl esters, then cooling a concentrated solution of the mixture. Methyl 2,5-dimethoxy-4-methylphenylacetate crystallized from the solution and was collected by filtration, then washed with cold methanol to remove any methylbenzoate. Hydrolysis of methyl 2,5-dimethoxy-4-methylphenylacetate with sodium hydroxide afforded 2,5-dimethoxy-4-methylphenylacetic acid.

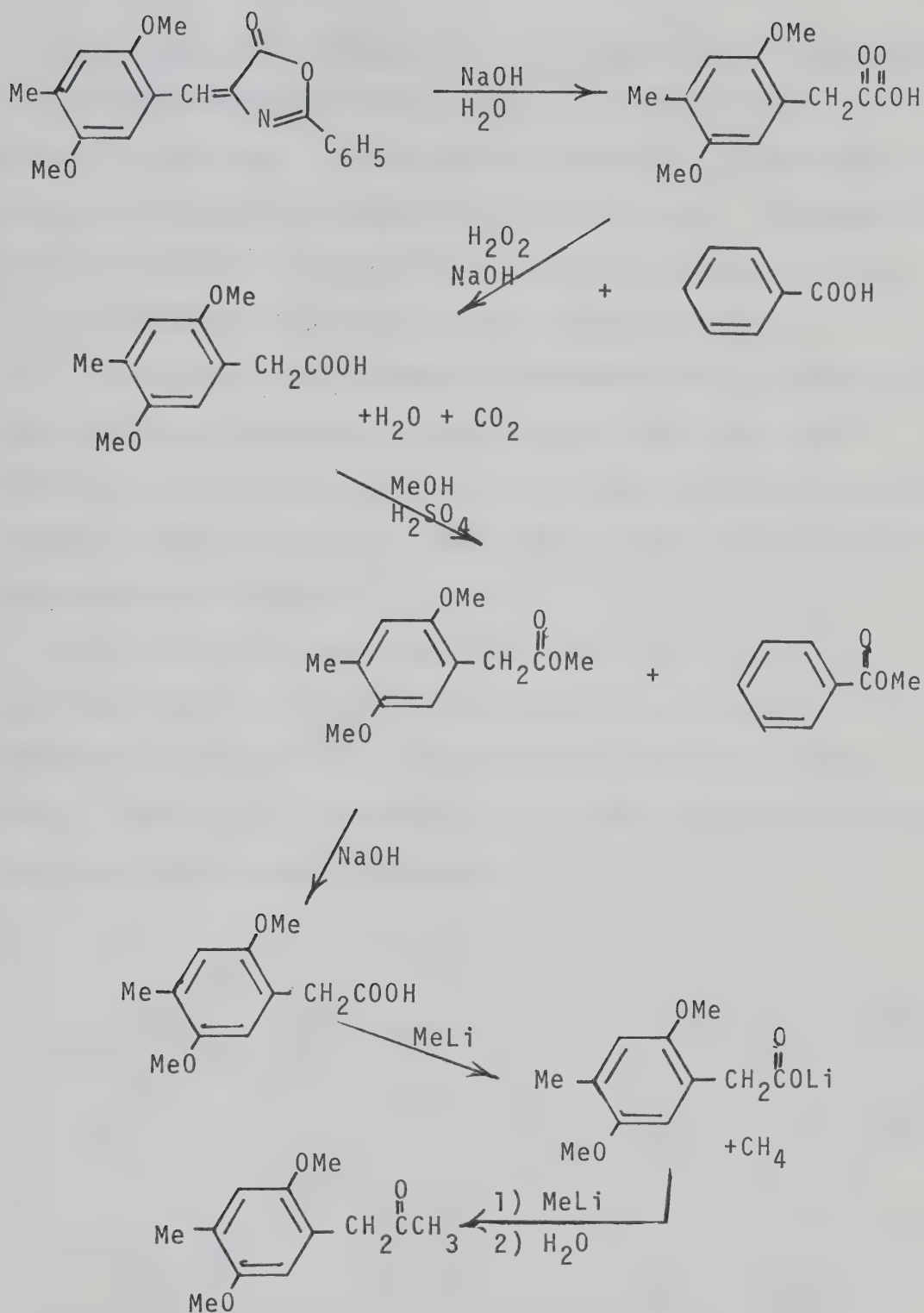
2,5-Dimethoxy-4-methylphenylacetone was prepared by treating 2,5-dimethoxy-4-methylphenylacetic acid with two equivalents of methyllithium⁽¹⁷³⁾. The first attempt to prepare the ketone (108b) involved the slow addition of an ethereal solution of methyllithium to a solution of the phenylacetic acid (108a) in ether. A poor yield of the

ketone was recovered. A modification of the procedure in which a solution of the acid (108a) was slowly added to the ethereal solution of methyllithium resulted in the formation of high yield of 2,5-dimethoxy-4-methylphenylacetone. The reaction sequence is shown in Scheme 22.

The preparation of the oximes (42) was undertaken by treating the phenylacetone (108b) with hydroxylamine hydrochloride. An oil was isolated. When a solution of this oil in ether was saturated with gaseous hydrogen chloride, a white solid slowly crystallized from the solution. The infrared spectrum of this material did not display a carbonyl absorption band at 1710 cm^{-1} . A very strong, broad absorbance band was present, however, at 2500 cm^{-1} . The molecular ion in the mass spectrum of the solid was located at m/e 233; also present were ions at m/e 36 and m/e 38 in the ratio of 3 to 1, suggesting the material was a hydrochloride salt. This was confirmed when a precipitate formed when an aqueous solution of the unknown was treated with a solution of silver nitrate. The ion of mass 223 corresponds to the formula $C_{12}H_{17}NO_3$, which agrees with the formula of the oxime (42). The fragmentation process of this molecule was unusual and will be discussed later (see page 106). The nmr spectrum was also consistent with structure (42).

The preparation of the hydroxylamine (41) has been discussed elsewhere (see page 98).

The synthesis of 1-(2,5-dimethoxy-4-methylphenyl)-2-

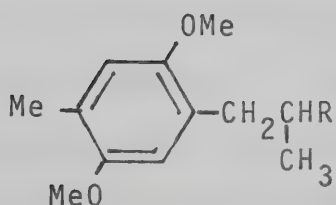
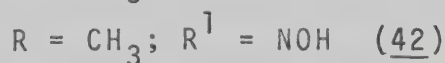
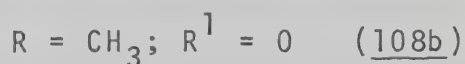
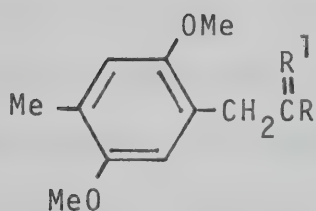


Scheme 22

propanol (93a) was attempted by hydrogenating a solution of 2,5-dimethoxy-4-methylphenylacetone in the presence of palladium-charcoal. The compound failed to incorporate hydrogen and starting material was recovered. Treatment of the same material (108b) with sodium borohydride yielded 1-(2,5-dimethoxy-4-methylphenyl)-2-propanol (93a).

N-Acetyl-1-(2,5-dimethoxy-4-methylphenyl)isopropylamine (39) was prepared by acetylating DOM with acetic anhydride. Since this material no longer possesses a basic nitrogen atom, it would be expected to be a poorly active psychotomimetic agent.

At this stage of the study, Ho et al. (101,102) published their studies on the metabolism of DOM. In another publication (103) it was shown that the activity of DOM was not due to a metabolite. In view of these findings the investigation was terminated.



e) Examination of Some of the Side Products Formed in a Synthesis of 1-(2,5-Dimethoxy-4-methylphenyl)isopropylamine (DOM)

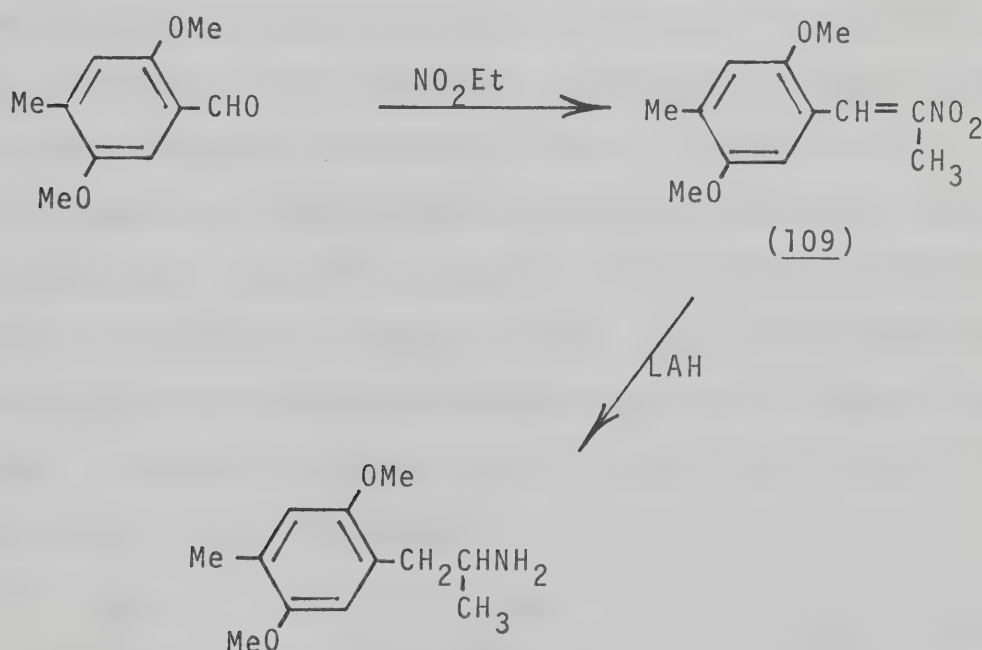
As discussed in the literature survey, some controversy concerning the potency and duration of action of STP existed when this drug originally appeared 'on the drug scene'. STP has since been found to contain the hallucinogenic drug 1-(2,5-dimethoxy-4-methylphenyl)isopropylamine. Some of the first reports describing the effects of STP indicated that it was much more potent and longer acting than an equivalent dose of pure 1-(2,5-dimethoxy-4-methylphenyl)isopropylamine (DOM). Since the exact reason for this extended duration of action of STP has never been resolved, the possibility that an additional synergistic component was present in STP samples was investigated.

The presence of several compounds in a 'street drug' can result from the mixing of another component with the pure drug, or from minor products introduced during the synthesis of the drug. Because of the limitless number of possible additives, an investigation of synergistic chemical combinations is impossible. It is, however, possible within reasonable limits to investigate the nature of the minor products produced in a synthesis of DOM. Apparently no investigation seeking pharmacologically active by-products in the synthesis of DOM or any other psychotomimetic phenethylamine has been undertaken. In view of the dramatic increase in the non-medical use of drugs, particularly

psychoactive drugs, any information concerning pharmacologically active contaminants becomes very important.

References in the literature^(14,37) claim that the original synthesis of DOM was accomplished by Shulgin in 1964^(11,174), but neither of these latter references mentions a synthesis of DOM. Although DOM has been the subject of numerous studies, its synthesis does not appear to have been reported in the literature.

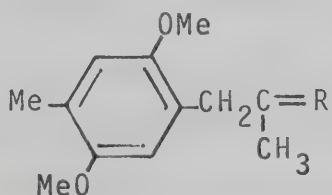
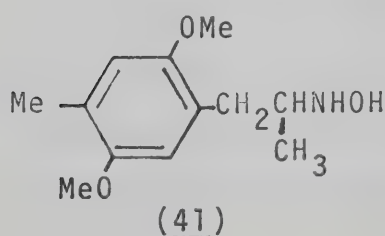
Because of the previously mentioned investigations of Shulgin as well as the availability of numerous literature references to the synthesis of phenylisopropylamines (see page 28), it is likely that DOM was originally prepared by the series of reactions shown in Scheme 23.



Scheme 23

Shulgin⁽¹⁷⁵⁾ has in fact reported the preparation of (109) as well as other 1-(dialkoxy-4-alkylphenyl)-2-nitropropenes-1 by this reaction. Although the reduction of the nitroolefin (109) can be easily accomplished by lithium aluminum hydride, it is a very expensive process. It may therefore be more feasible for a poorly equipped, economy minded "underground" laboratory to undertake the reduction by a cheaper, alternate route. The present study concentrated on identifying the minor products from the reduction of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene-1.

A summary of the various products recovered following the reduction of 1-phenyl-2-nitropropene-1 and related compounds employing a variety of reducing conditions has been presented in the literature survey. It is possible that similar reduction products, namely (41), (42), (108b), and (110), could be present following a reduction of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene-1. Some of these possible reduction products could possess psychotomimetic properties. Compounds (41), (42), and (108b) have previously been considered as possible active metabolites of DOM. Compound (110) is not unlike DOM and is also a potentially active compound.



R = O (108b)

R = NOH ((42))

R = NH (110)

Since one can only speculate on a possible synthetic route in the preparation of DOM by an "underground" laboratory, it was decided that a reduction of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene-1 would be undertaken using a very common reducing system, namely palladium and hydrogen. It was not intended to develop reduction conditions to obtain high yields of the above products but rather only to see if they were present.

The preparation of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene-1 was undertaken by heating a solution of 2,5-dimethoxy-4-methylbenzaldehyde, nitroethane, and ammonium acetate in acetic acid. An ethanolic solution of the purified nitropropene was then hydrogenated at room temperature and pressure in the presence of palladium-charcoal. Initially hydrogen was incorporated rapidly, then the rate slowly decreased. When it appeared that uptake had ceased, the reaction flask was removed from the hydrogenation apparatus; a strong odor of ammonia was discerned. When moistened red litmus paper was placed above the reaction mixture, it turned blue. The mixture was then stirred at room temperature until the evolution of ammonia ceased, and then hydrogenated further. An additional amount of hydrogen was incorporated. Removal of the solvent left an oily material which was positive to 2,4-DNP reagent. The infrared spectrum of this material displayed a strong absorption band near 1710 cm^{-1} and a broad peak at 3300 cm^{-1} .

Solvent extraction yielded two basic compounds, i.e DOM and a compound displaying an OH absorption band near 3100 cm^{-1} as well as peaks characteristic of a primary amine salt. The mass spectrum of this material had a molecular ion present at m/e 225 corresponding to the formula $\text{C}_{12}\text{H}_{19}\text{NO}_3$ which fits structure (41). Both of these products were obtained in relatively low yield.

The infrared spectrum of the reaction product after removal of the basic components suggested the presence of the phenylacetone (108b) as well as the corresponding oxime (42). In an attempt to separate these components, an ether solution of the mixture was saturated with hydrogen chloride gas. An oil separated from solution. The solvent was removed and the mixture was crystallized to yield the hydrochloride of the oxime of 2,5-dimethoxy-4-methylphenylacetone as well as 2,5-dimethoxy-4-methylphenylacetone itself.

The hydrogenation of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene-1 was repeated, except that a small amount of hydrochloric acid was added to the ethanol. The evolved ammonia was expected to react with the acid, thereby not interfering with the uptake of hydrogen. Hydrogen was taken up rapidly, then suddenly ceased, unlike the slow 'tailing off' previously observed. Removal of the catalyst and solvent left an oil which was positive to 2,4-DNP reagent. The infrared spectrum of the oil showed that the peak at 1710 cm^{-1} was not very strong, indicating the ketone was not

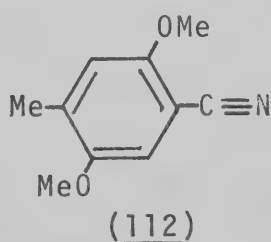
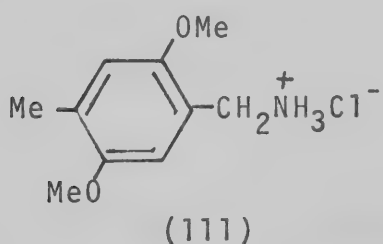
the major product. A very broad band was present at 2550 cm^{-1} , characteristic of a tertiary amine salt, and no absorbances were present above 3000 cm^{-1} . The oil slowly crystallized to yield the hydrochloride salt of the oxime of 2,5-dimethoxy-4-methylphenylacetone. Although the mixture was not completely separated it appears the oxime is the major reaction product.

A study of the reaction products following the reduction of a crude sample of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene-1 was also undertaken. It appeared that at least one other component different from the starting material or 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene-1 was present in the crude product isolated from the reaction of 2,5-dimethoxy-4-methylbenzaldehyde and nitroethane. This was evident by the presence of a strong absorption band at 2210 cm^{-1} in the infrared spectrum of the crude reaction product. Although this absorption band is indicative of a $\text{C}\equiv\text{N}$ group, the structure possessing this functional group was not obvious.

When a sample of this crude reaction product was hydrogenated as previously described, hydrogen was slowly absorbed for a significant time after the rapid phase of hydrogen incorporation ceased. A crystalline material with a melting point different from any material previously isolated was recovered from the reaction mixture. The infrared spectrum of this solid displayed bands character-

istic of a primary amine salt. Present in the nmr spectrum were: 2-aromatic protons, three 3-proton singlets (i.e. the 2- and 5- OCH_3 groups and the 4-methyl group), a broad 3-proton signal which exchanged with deuterium oxide, and a 2-proton singlet. This spectral evidence fits 2,5-dimethoxy-4-methylbenzylamine hydrochloride (111). The molecular ion in the mass spectrum of the compound was located at m/e 181, which is the molecular weight of (111). The elemental analysis also corresponded to 2,5-dimethoxy-4-methylbenzylamine hydrochloride; therefore it was concluded that structure (111) was the correct assignment for this material.

It thus appeared likely that 2,5-dimethoxy-4-methylbenzylamine was derived from 2,5-dimethoxy-4-methylbenzonitrile. This assumption was confirmed when a pure sample of 2,5-dimethoxy-4-methylbenzonitrile (112) was isolated from the crude sample of the nitropropene. In addition to infrared (2210 cm^{-1}) and nmr spectral data, the elemental analysis was consistent with this structure.

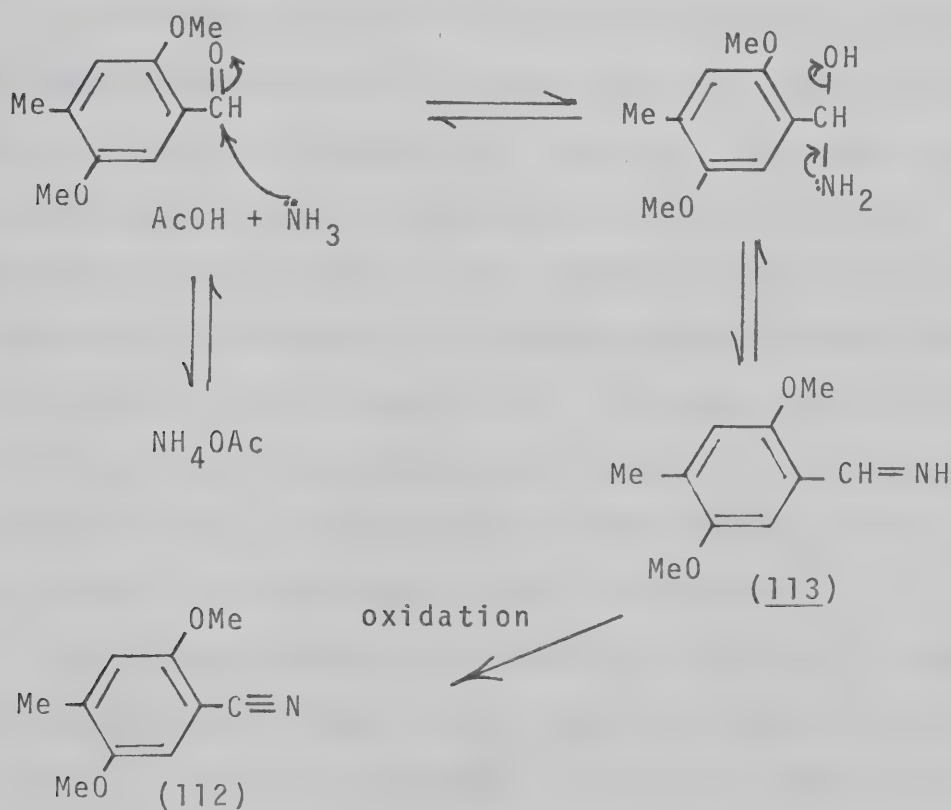


An infrared spectrum was recorded for each of the starting materials used in the reaction in which the nitrile was found. None showed an absorption near 2210 cm^{-1} ; this

confirmed (112) was formed as a reaction product.

Heating benzaldehydes, nitroethane, and ammonium acetate in acetic acid has been a preparative method for the synthesis of many nitropropenes. It appears, however, that no other studies have been reported identifying this type of product (benzonitrile) from the reaction of other benzaldehydes under identical conditions.

Although the mechanism of formation of the benzonitrile is not obvious, it could be formed as suggested by Scheme 24. In such a mechanism free ammonia must be present in order to form the Schiff base (113); this would then presumably be oxidized to the nitrile (112).



Scheme 24

When the same reaction was undertaken in the absence of nitroethane, the infrared spectrum of the crude reaction mixture failed to display $\text{C}\equiv\text{N}$ stretching at 2210 cm^{-1} . Therefore it appears nitroethane plays an active role in the formation of (112). Its function may be that of an oxidizing agent much like that of nitrobenzene in the Skraup synthesis of quinoline⁽¹⁷⁶⁾.

Based on the structure-activity relationship studies of methoxylated phenethylamines, it is unlikely that (111) would possess any psychotomimetic properties. It is, however, toxicologically important because of its other possible pharmacological effects.

Kudrin and Koroza⁽¹⁷⁷⁾ studied some methoxylated benzylamine derivatives and found that they contracted the uterus of rabbits, guinea pigs, and rats. The most potent of the structures they investigated was found to be 2,5-dimethoxybenzylamine. They reported that the rat uterus was much more sensitive to 2,5-dimethoxybenzylamine than to the very potent drug ergometrine. Although the pharmacology of 2,5-dimethoxy-4-methylbenzylamine was not undertaken in the present study, it seems likely that it would have the same ability to stimulate uterine contractions.

It is conceivable the highly abused drug 3,4-methylenedioxyamphetamine (MDA) could also be prepared employing the aforementioned reaction conditions, i.e. heating a solution of 3,4-methylenedioxybenzaldehyde, nitroethane, and

ammonium acetate in acetic acid, then reducing the reaction product with lithium aluminum hydride. When this condensation reaction was undertaken, a mixture of products was recovered. The infrared spectrum of the mixture indicated that starting aldehyde and nitropropene, as well as benzonitrile, were present. In an attempt to separate the components the mixture was distilled under reduced pressure. Although 1-(3,4-methylenedioxyphenyl)-2-nitropropene-1 was separated from the mixture, the aldehyde and benzonitrile distilled together over a wide range. To determine the amount of benzonitrile present in the mixture, the distillate containing the benzonitrile was reduced with lithium aluminum hydride. The resulting 3,4-methylenedioxybenzylamine was extracted from the mixture. The yield of this product, although low, was significant.

A complete separation of the products of each of the reductions described in this study was not achieved and the possibility of other potentially active compounds cannot be discounted.

f) Analysis of Two Samples of 'Street STP'

In an attempt to determine whether any of the potentially active by-products which could arise in a synthesis of DOM were present in illicit samples of DOM, two samples of 'street STP' were analyzed. Both were police-seized and were of different origins (these will be referred to as

samples A and B). They were each subjected to an extraction procedure⁽¹⁷⁸⁾ whereby the basic and neutral components were separated. A mass spectrum of both basic extracts was then recorded and examined for the presence of ions at m/e 225, 223, 208, 207, and 181, which correspond to the molecular ions of structures (41), (42), (108b), (110), and (111) respectively. None, however, was present. The spectrum contained ions which undoubtedly could be attributed to DOM and its expected fragmentation products⁽¹⁷⁹⁾ but, in addition, other extraneous ions not originating from DOM were present in both spectra.

In the mass spectrum of a basic extract of sample A fragments were present at m/e 193 and 192 in significant abundance. Accurate mass determination revealed that the molecular formulae of these ions were $C_{10}H_{15}N_3O$ and $C_{10}H_{14}N_3O$ respectively. It appears that $C_{10}H_{15}N_3O$ fragments with the loss of a hydrogen atom to $C_{10}H_{14}N_3O$, which in turn might fragment further to the abundant ion of m/e 149. A survey of the literature revealed that numerous compounds possess formula $C_{10}H_{15}N_3O$, and since the compound which produced these ions was not isolated, the exact identity of this material was not determined.

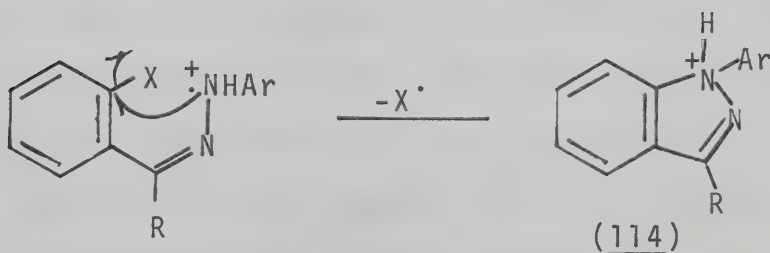
In the mass spectrum of the basic extract of sample B, an ion of m/e 265 was present in addition to ions originating from DOM. This ion was of low abundance (<2%). An accurate mass measurement revealed this ion had the formula $C_{15}H_{23}NO_3$.

This compound was not identified.

In addition to the mass spectral studies, a comparison of the thin layer chromatographic behavior of the basic and neutral extracts of A and B as well as structures (41), (42), (108b), and (111) was undertaken. Unfortunately, a solvent system in which these compounds had different R_f values was not found. However, after examination of the thin layer plates under ultraviolet light, or after spraying with 2,4-DNP reagent, it was clear that compounds (41), (42), (108b), and (111) were absent from samples A and B. These studies also confirmed that more than one basic component was present in both A and B.

g) The Mass Spectra of Some Possible Metabolites of DOM

Cable et al.⁽¹⁸⁰⁾ reported recently that the mass spectra of phenylhydrazones of ortho-substituted benzaldehydes and acetophenones show characteristic $[M-X]^+$ ions when the ortho-substituent, X, was I, Br, Cl, OH, and OCH₃. These workers postulated that the five-membered ring structure (114) formed concurrently with the expulsion of X.



The formation of a large $[M-Cl]$ has also been observed⁽¹⁸¹⁾ in the mass spectra of o-chlorophenylureas, thioureas, and carbamates.

The present study investigated the behavior of the two oximes (42) and (82) upon electron impact (see figures 1 and 2). These were observed to undergo similar ortho-effects. Unlike the low abundance of the $[M-31]$ ions formed in the o-methoxy derivatives studied by Cable, the $[M-31]$ ions in the mass spectra of these oximes were prominent. Accurate mass measurements identified the $[M-31]$ fragment as $[M-OMe]^+$. Hence it seemed likely that the cyclic nitronium ion (115) had formed.

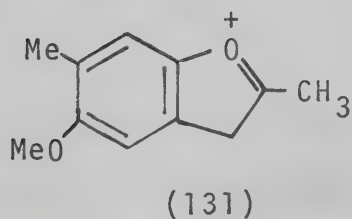
Coutts and Mukherjee⁽¹⁸²⁾ have observed that aromatic hydroxylamines fragment by expelling an oxygen atom and a hydroxyl radical. The cyclic nitronium ion (115) behaved similarly on electron impact, producing (116) and (117). The transition in which the hydroxyl radical is lost involves the formation of an odd-electron ion (117) from the even-electron ion (115). Although this is energetically unfavorable, a metastable ion supports this fragmentation pathway.

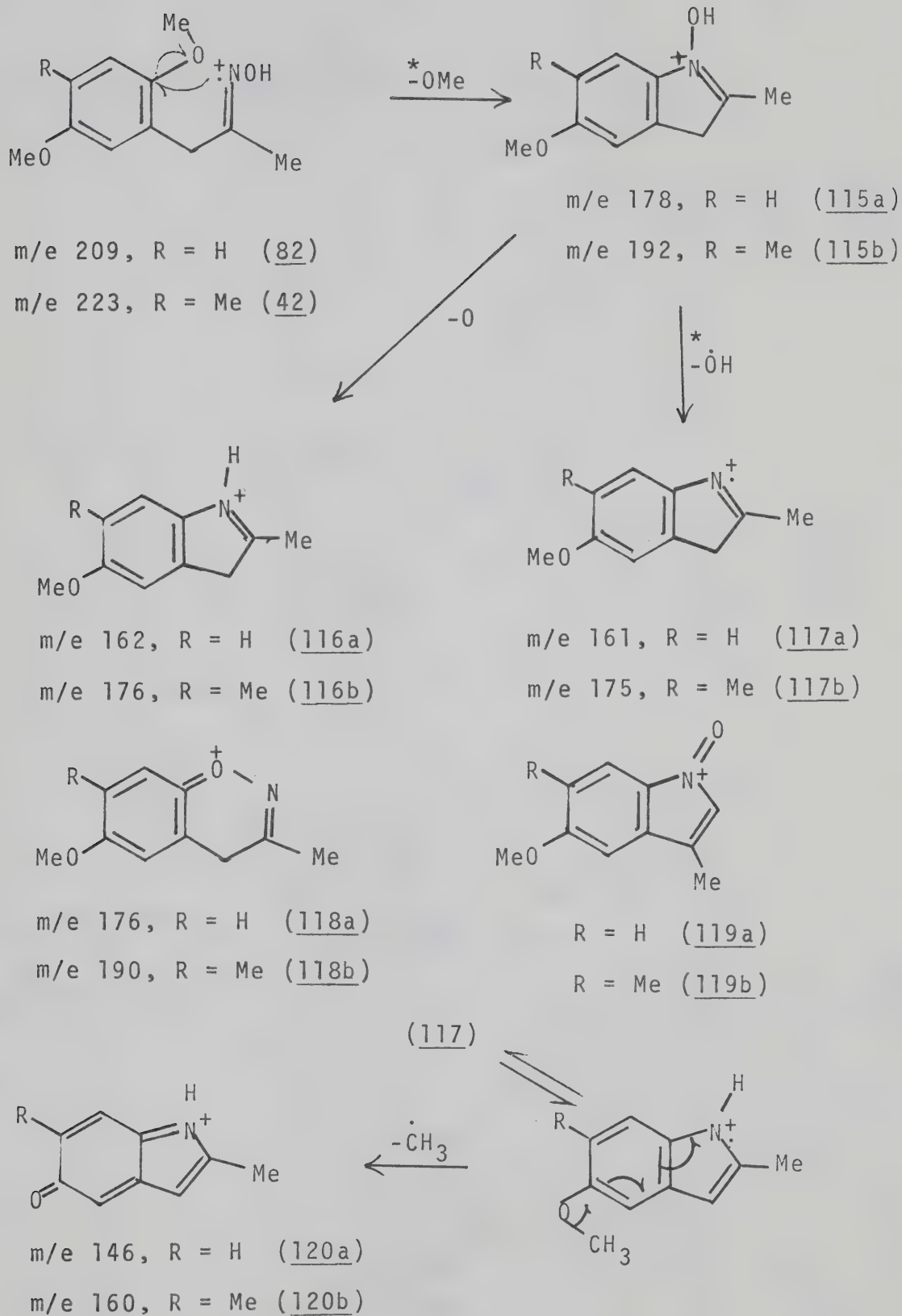
An additional fragment ion $[M-33]$ was present in both spectra. Although it is not clear how these ions originate, it is possible they can also form as a result of this ortho-effect. Structures (118) and (119), for instance, can accommodate the loss of 33 mass units.

In addition to the aforementioned fragment ions, numerous other ions of significant abundances were present in both spectra. These ions are thought to originate from further fragmentation of the cyclic intermediates described and from fracture of the side chain of the oxime. Possible mechanisms to explain their formation are presented in Scheme 25.

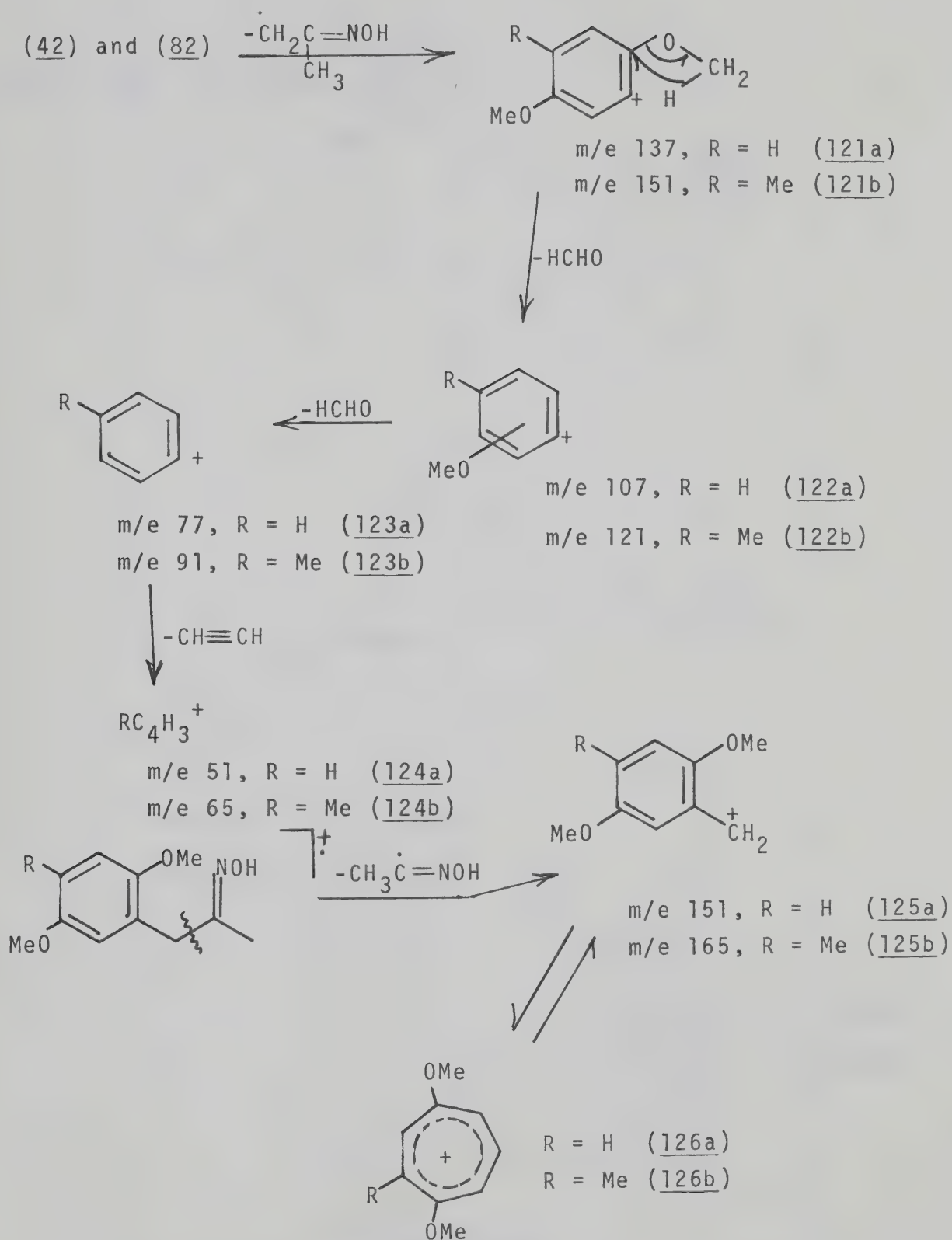
To determine whether the ortho-effect was a general reaction and of any value in the identification of some methoxylated phenethylamines or their metabolites, the mass spectra of two possible metabolites of DOM as well as a related hydroxylamine were next investigated.

The first mass spectrum examined was that of 2,5-dimethoxy-4-methylphenylacetone (108b) (see Figure 3). By analogy with (42) or (82), this compound might be expected to expel the ortho-methoxy group on electron impact and yield the cyclic oxonium ion (131). This, however, did not occur. Instead, the molecule fragmented in a manner typical of benzyl ketones⁽¹⁸³⁾ and yielded the benzylium (125) or tropylium (126) ion as well as an ion of mass m/e 43 (132).

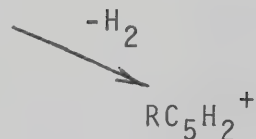
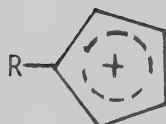
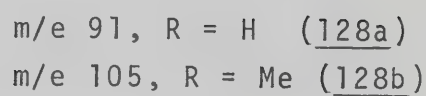
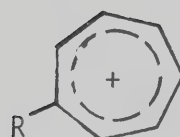
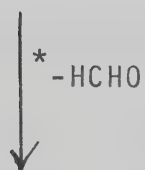
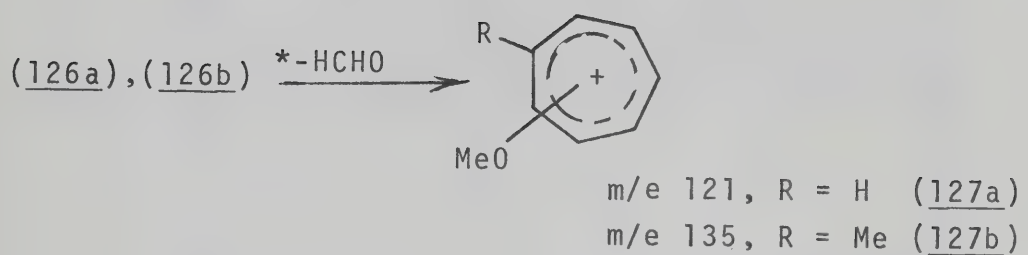




Scheme 25



Scheme 25 cont.



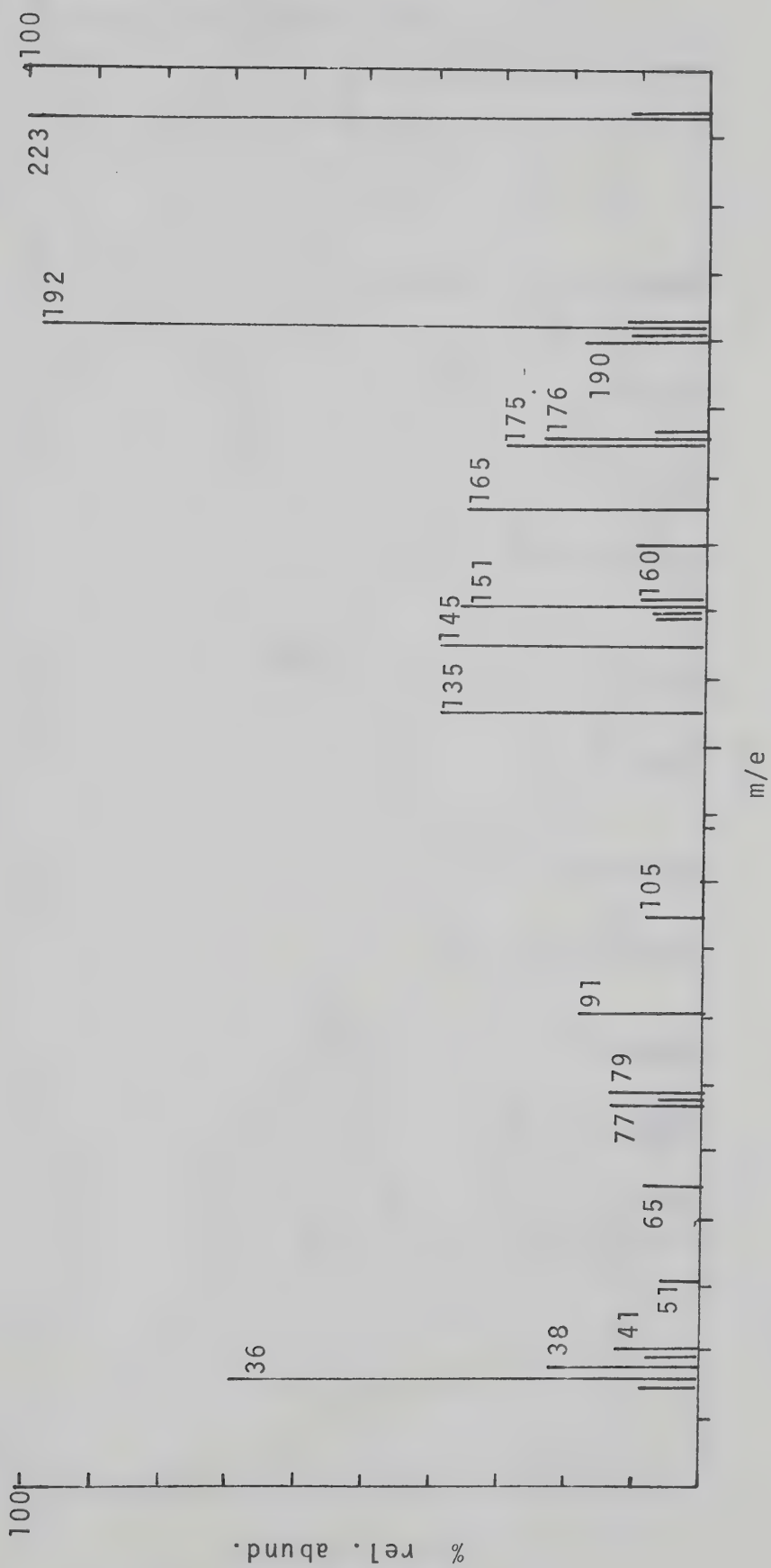
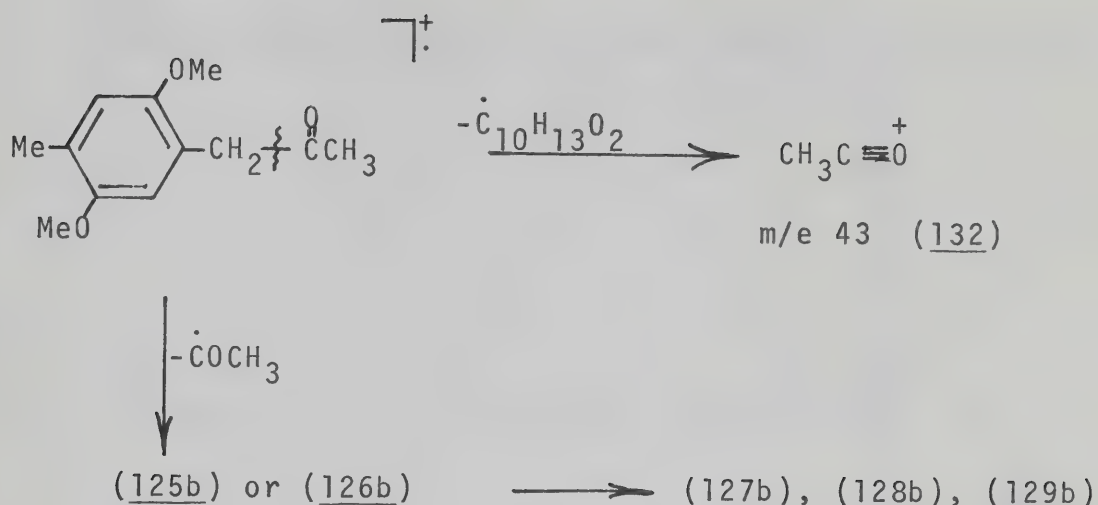


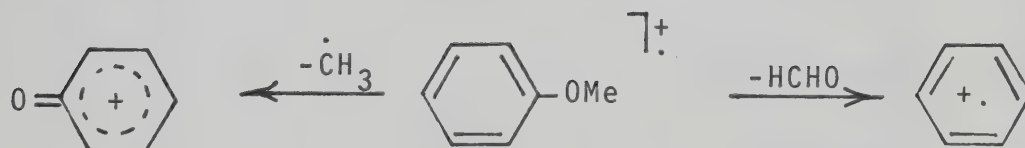
Figure 1: Mass spectrum of the oxime of 2,5-dimethoxy-4-methylphenylacetone



Figure 2: Mass spectrum of the oxime of 2,5-dimethoxyphenylacetone



Aromatic methyl ethers commonly fragment at the methoxy group by expelling either a methyl radical or a formaldehyde radical⁽¹⁸⁴⁾:



Other studies have shown that the aromatic ring in benzenoid compounds ejects one or more molecules of acetylene when it fragments⁽¹⁸⁵⁾.

The benzylium ion (125b) fragmented with the successive expulsion of HCHO, HCHO, and CH $\equiv$ CH to yield (127b), (128b), and (129b) respectively in the manner illustrated in Scheme 25.

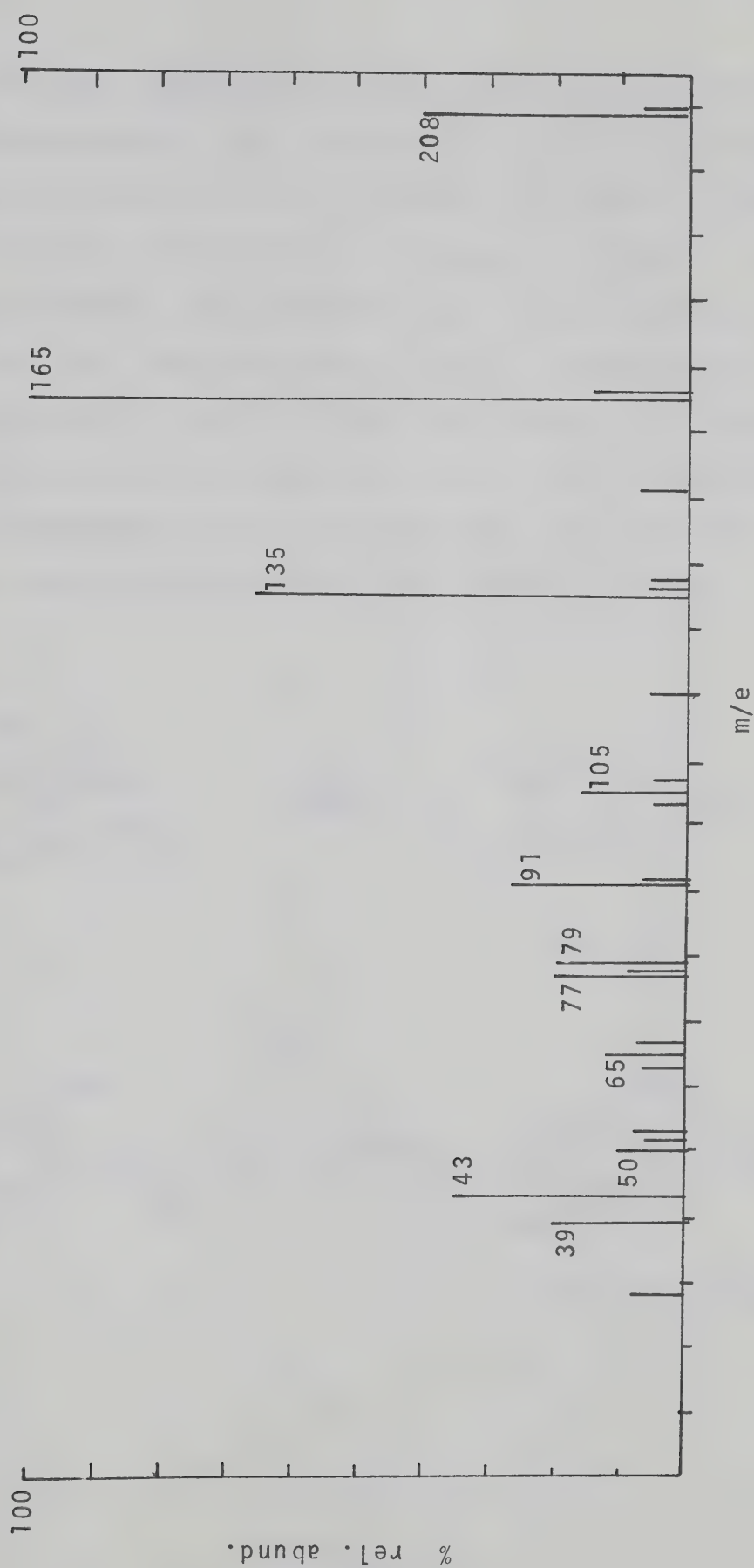
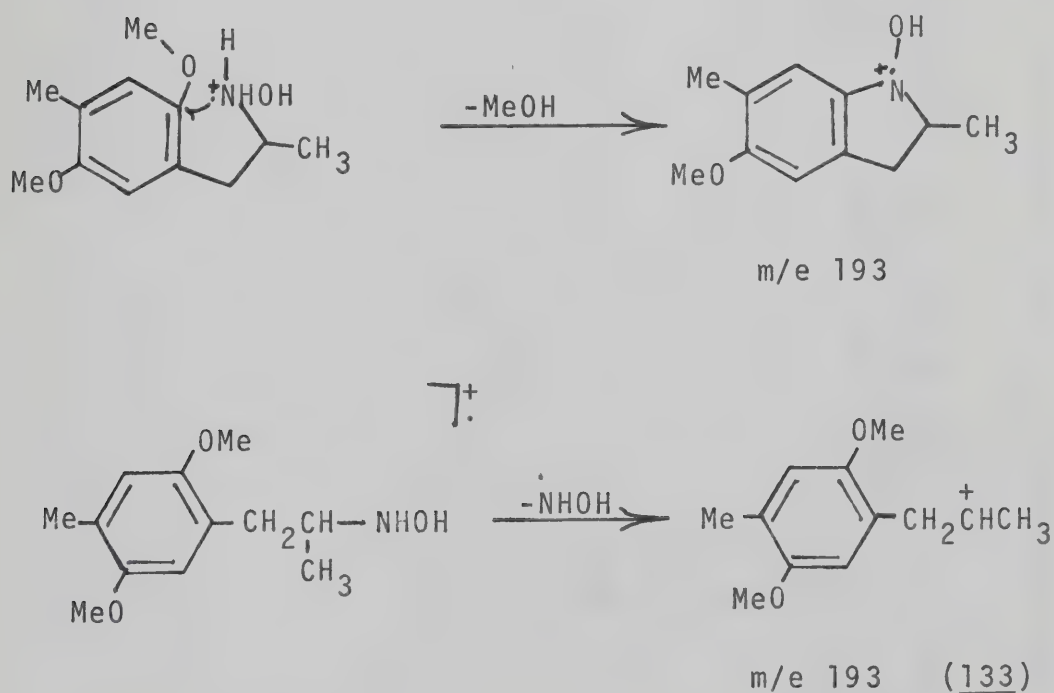


Figure 3: Mass spectrum of 2,5-dimethoxy-4-methylphenylacetone

The mass spectrum of N-(2,5-dimethoxy- α ,4-dimethylphenethyl)hydroxylamine, (41) (Figure 4) was next investigated. The expulsion of a 31 a.m.u. fragment on electron impact also failed to occur with this compound. Present in this spectrum, however, was an [M-32] ion in low abundance. Since this ion can originate via either of two mechanisms, i.e. expulsion of CH_3OH or $\cdot\text{NHOH}$ (see below), an accurate mass measurement of the m/e 193 ion was made. This identified the fragment ion as $\text{C}_{12}\text{H}_{17}\text{O}_2$ (133) and confirmed that the m/e 193 ion resulted from the expulsion of $\cdot\text{NHOH}$.



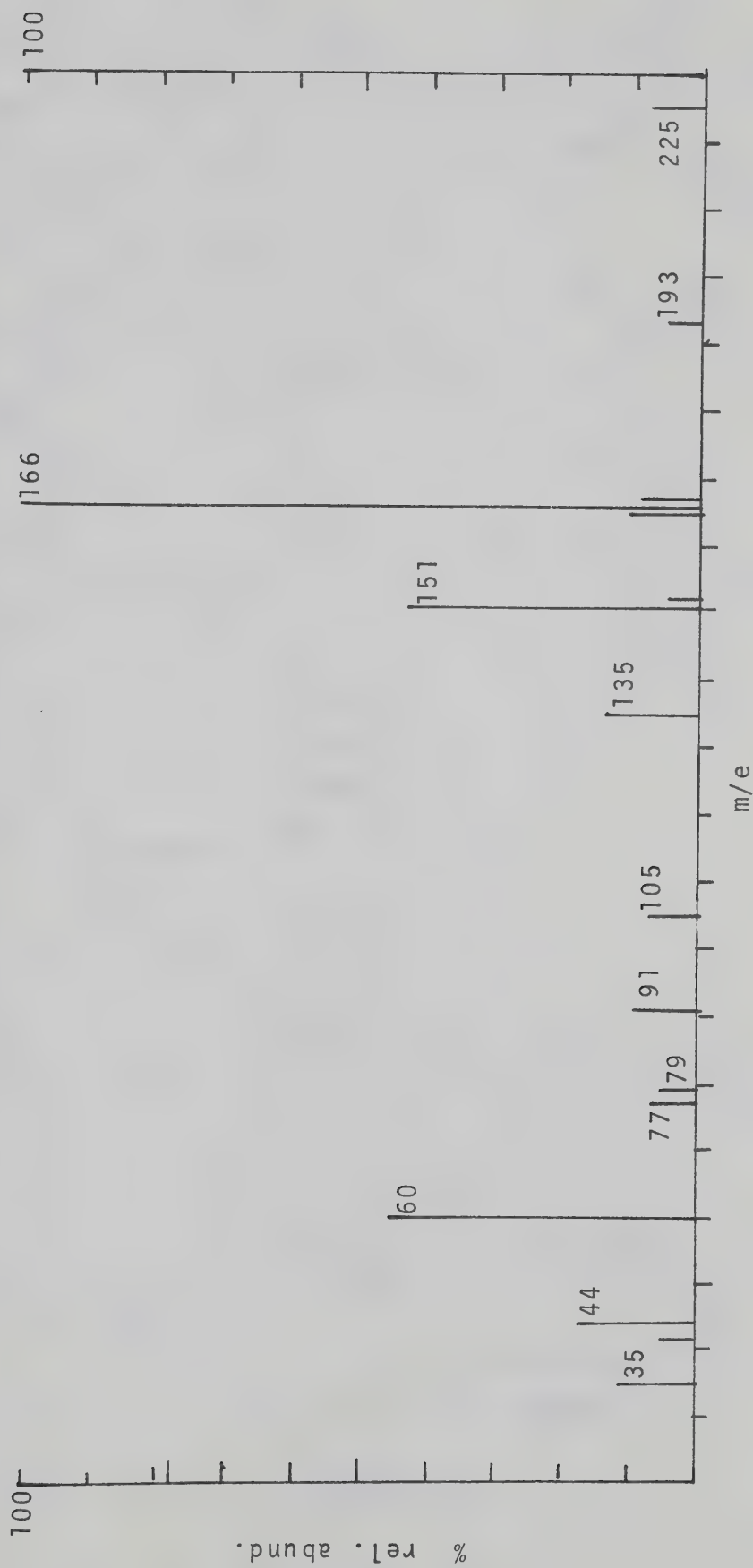
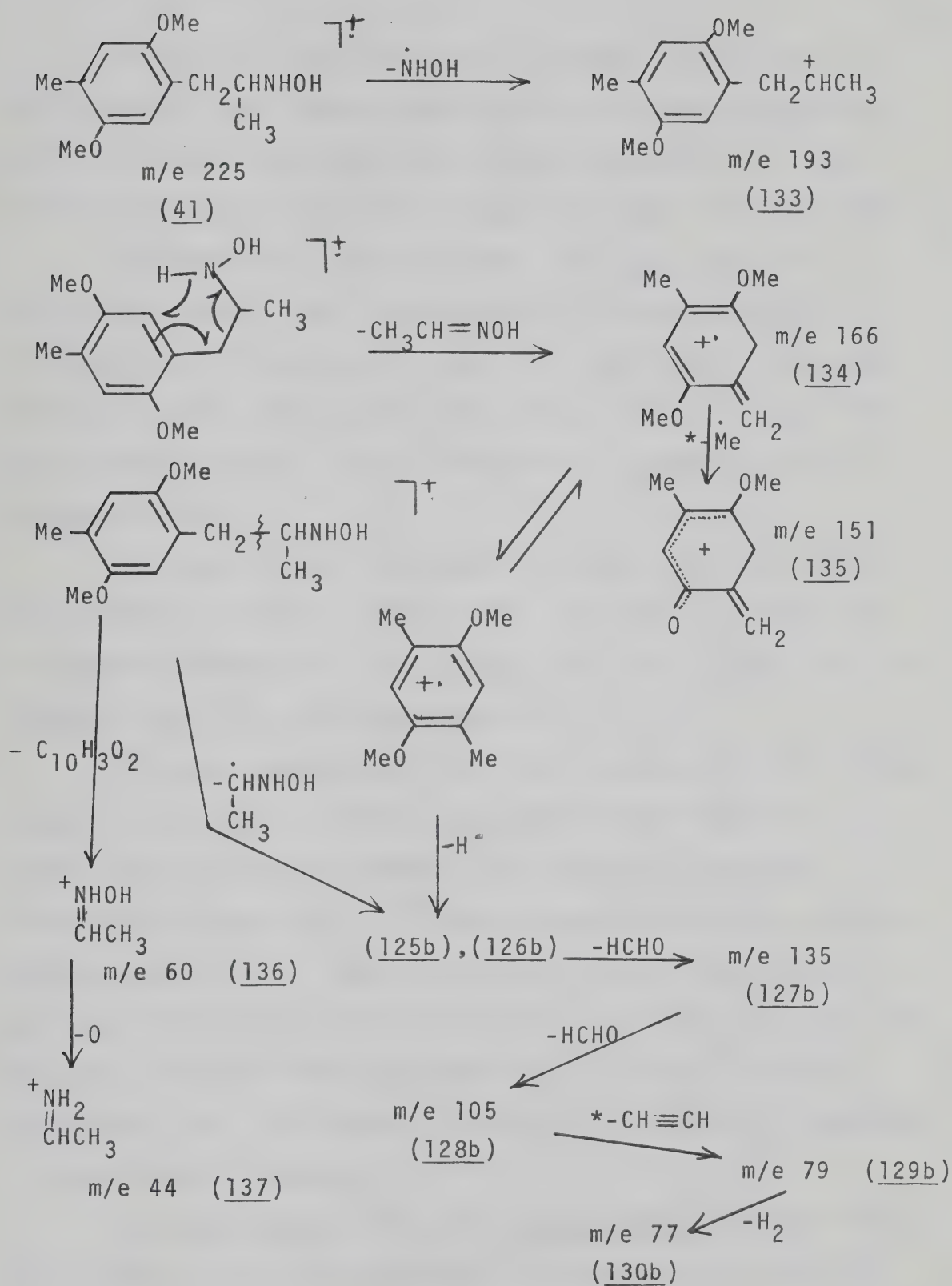


Figure 4: Mass spectrum of N-(2,5-dimethoxy- α ,4-dimethylphenethyl)hydroxylamine



Scheme 26

To explain the presence of abundant ions at m/e 60 and m/e 44, these masses were also accurately measured and were identified as C_2H_6NO and C_2H_6N respectively. These ions are shown by structures (136) and (137) in Scheme 26.

Formation of the ion at m/e 166 (134) from the molecular ion (41) can be envisaged through a McLafferty rearrangement (Scheme 26). This ion (134) then fragmented further to the stable even-electron ion (135) by expulsion of a methyl radical. This transition is supported by a metastable ion.

The ion at m/e 165 (125b) or (126b) can arise by two mechanisms as shown in Scheme 26. This even-electron ion fragmented further to yield (127b), m/e 135; (128b), m/e 105; (129b), m/e 179; and (130b), m/e 77.

The mass spectrum of the lower homolog of the previous example, i.e. N-(2,5-dimethoxy-4-methylphenethyl)hydroxylamine (87b) was next examined. As would be expected, it fragmented (Figure 5) in a manner analogous to the previous hydroxylamine (41). However, unlike the previous example, an ion of $[M-16]$ was also present in the spectrum. This was thought to result from the expulsion of oxygen from the molecular ion. The manner in which this molecule fragmented is outlined in Scheme 27.

It thus appears that the ortho-effect observed with the oximes is not a general reaction and is of no utility for the aforementioned purpose.

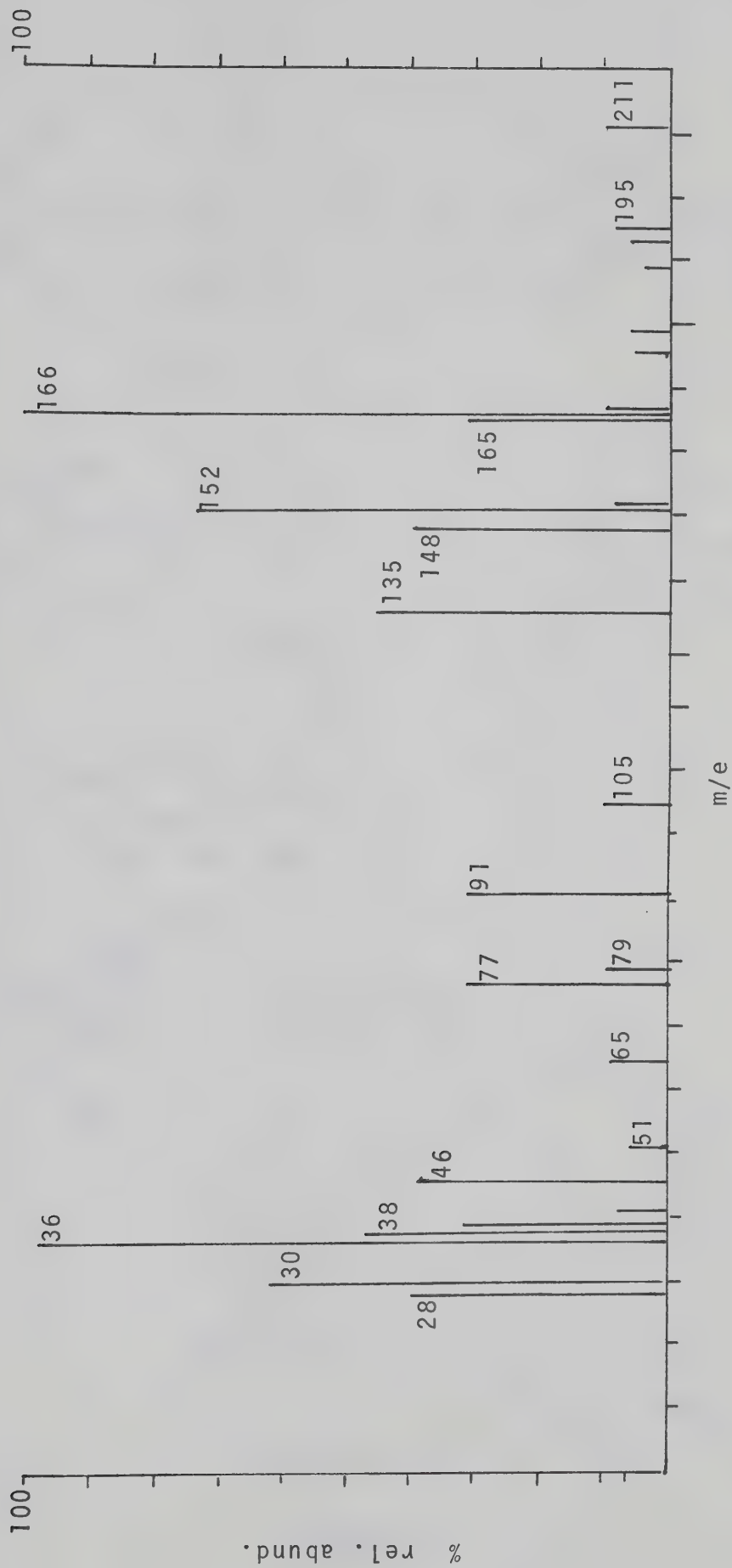
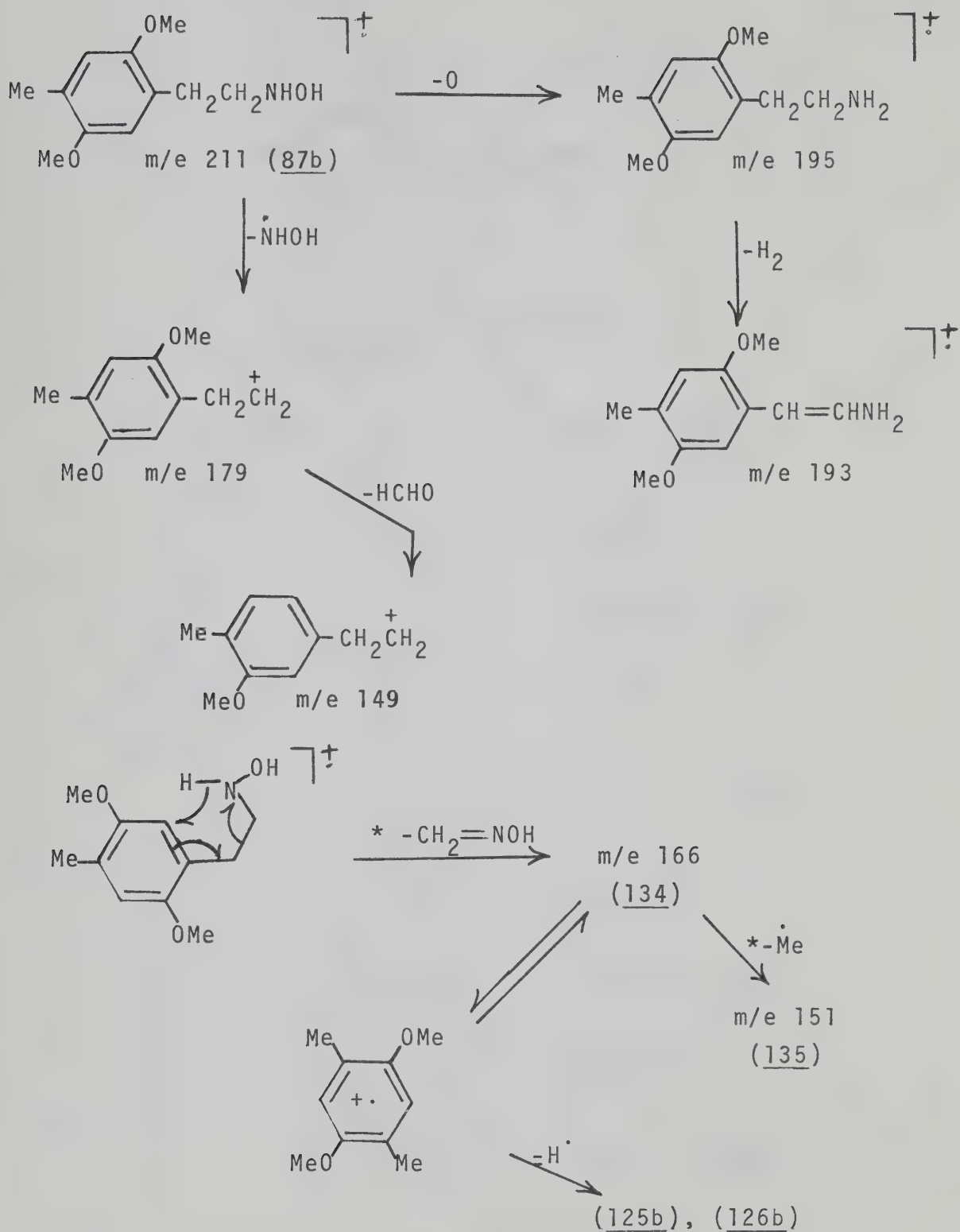
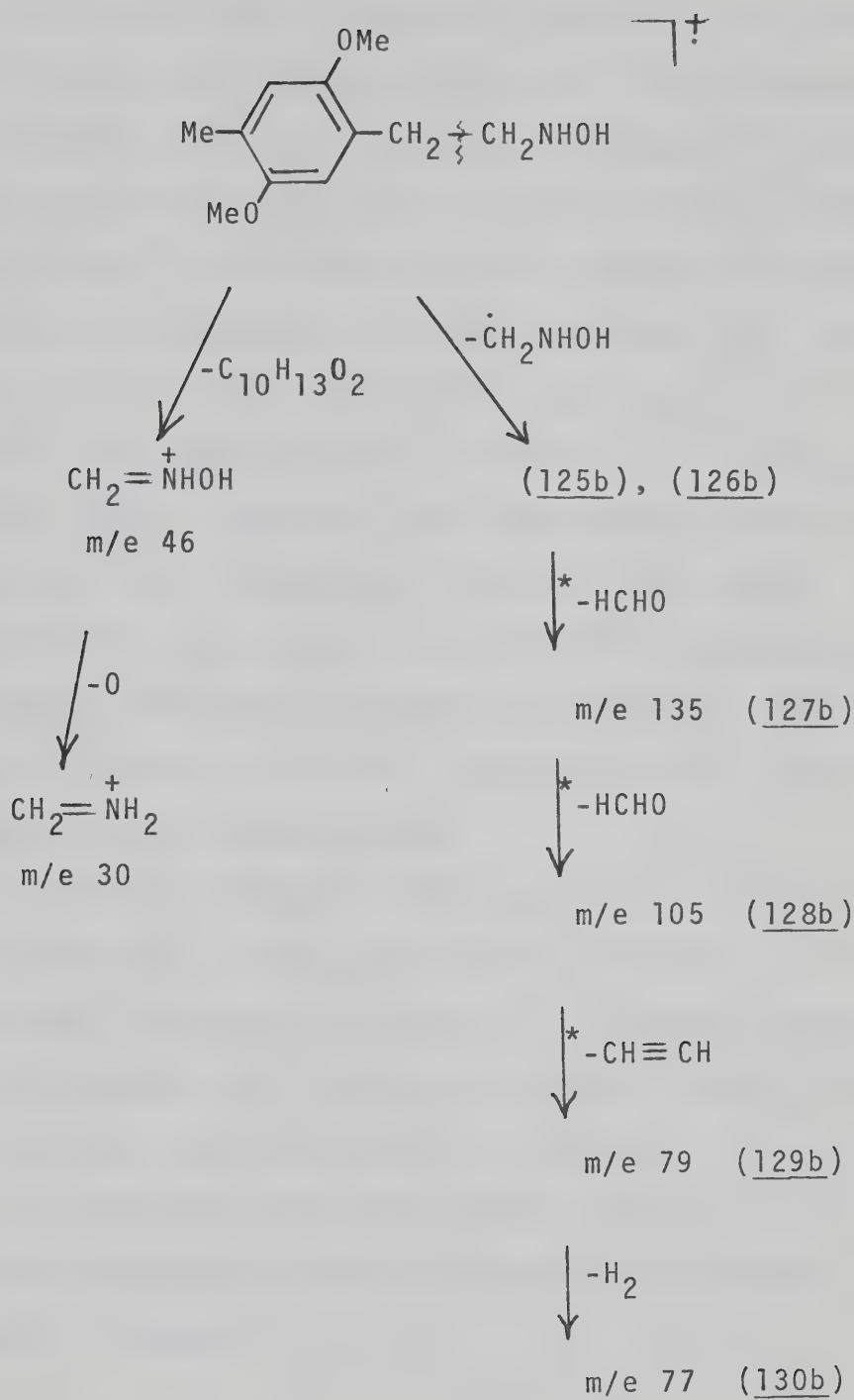


Figure 5: Mass spectrum of N-(2,5-dimethoxy-4-methylphenethyl)hydroxylamine



Scheme 27

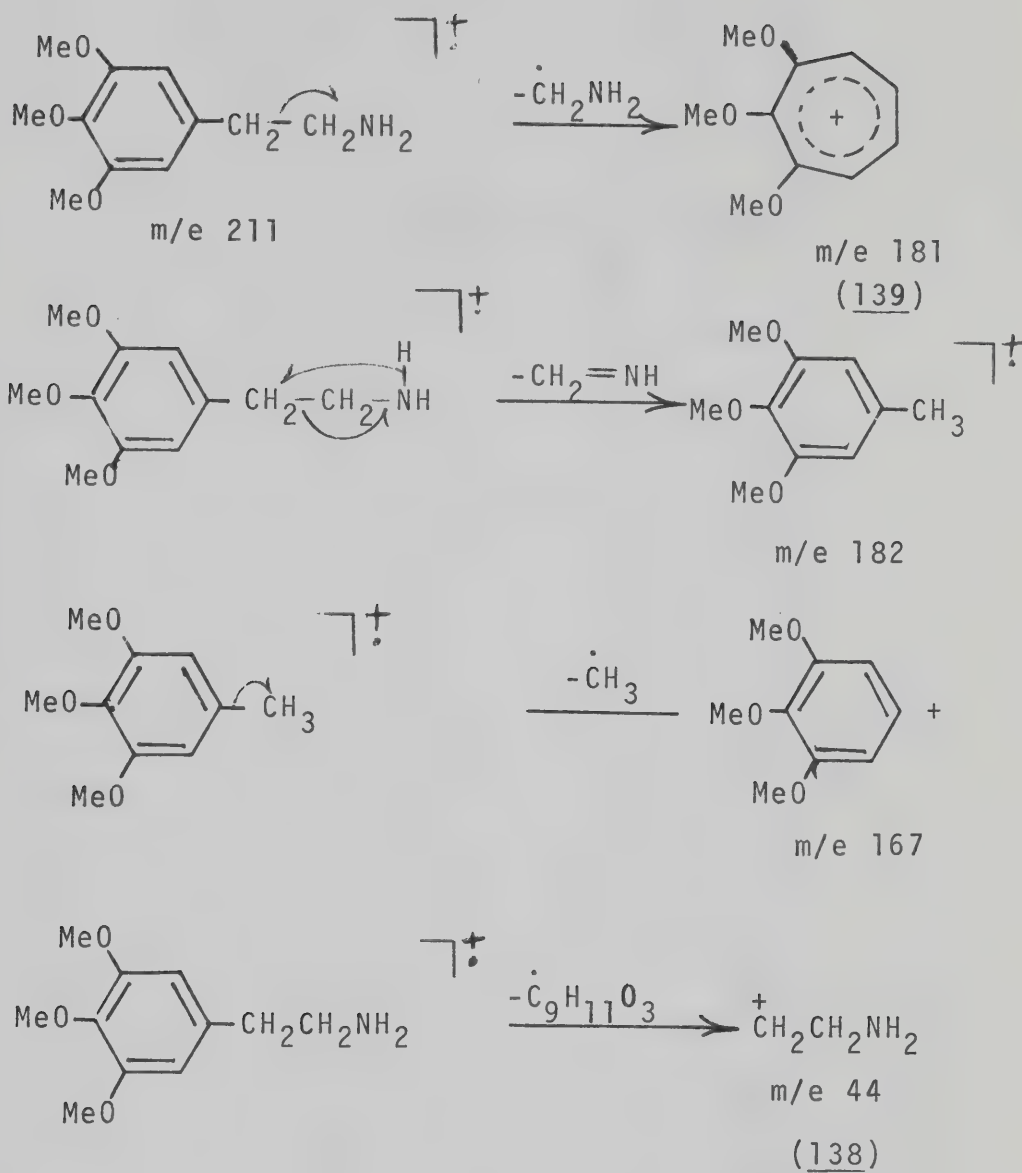


Scheme 27 cont.

A survey of the literature showed that few mass spectral studies of phenethylamines or the corresponding hydroxylamines had been undertaken. Bellman⁽¹⁷⁹⁾ reported the mass spectra of some hallucinogenic drugs including DOM and mescaline. On the basis of his evidence, he concluded that mescaline fragmented as shown by Scheme 28. He reported that the base peak in the mass spectrum was located at m/e 44. He identified this fragment ion as that shown by structure (138). Although the fragmentation pathway which yielded this ion is possible, it seems very unusual that it would yield the base peak. Normally⁽¹⁸⁶⁾ amines undergo α -cleavage as the major fragmentation pathway. Therefore, either of the ions at m/e 181 (139) or m/e 30 (140) would be expected to be the base peak.

To confirm Bellman's finding that the ion at m/e 44 was the base peak, a mass spectrum of mescaline hydrochloride was recorded and examined (Figure 6). Contrary to the reported evidence, the ion at m/e 44 was virtually non-existent. The base peak was present at m/e 30.

To supplement Bellman's interpretation of how mescaline fragments on electron impact, the summary is presented in Scheme 29.



Scheme 28

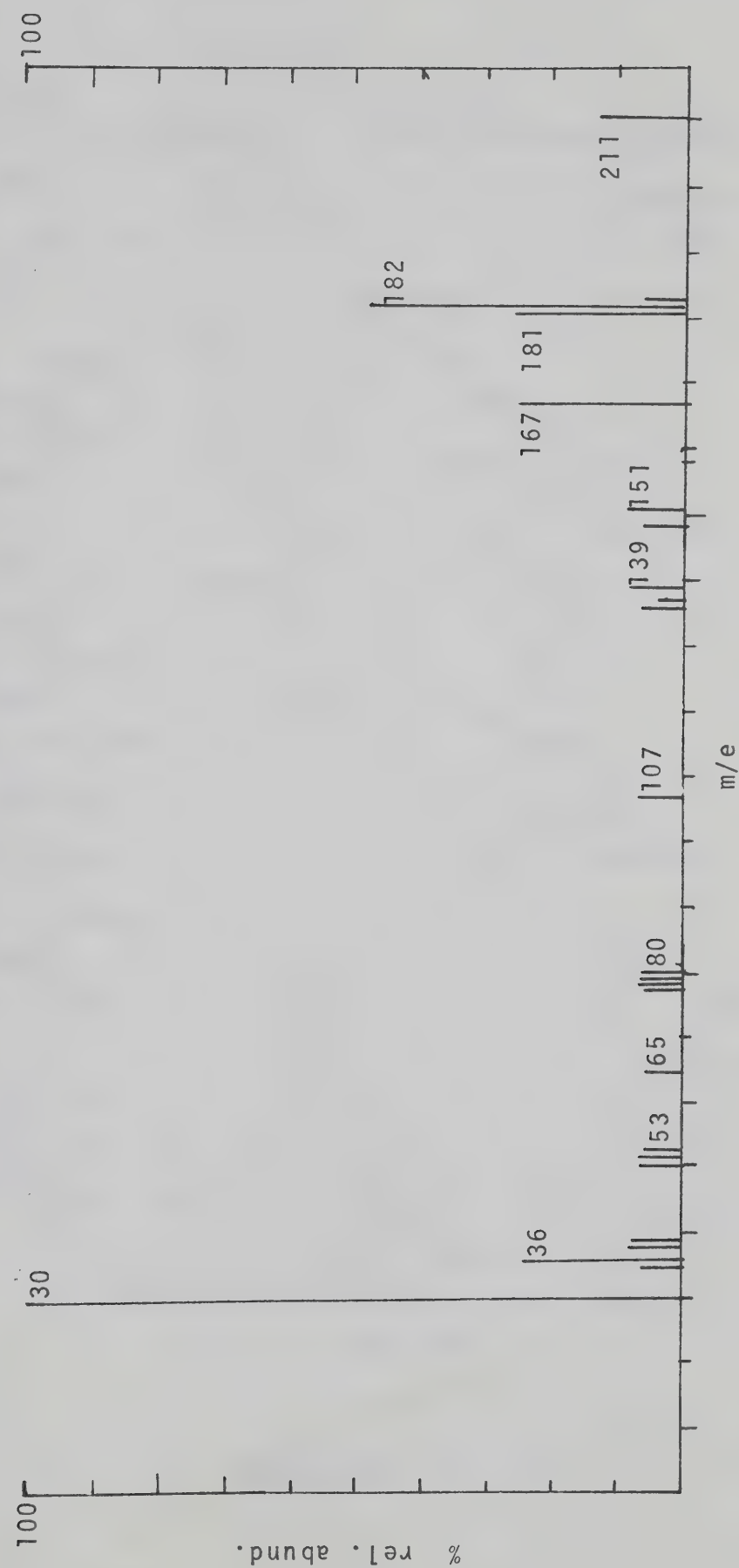


Figure 6: Mass spectrum of mescaline hydrochloride

II.

AMINOINDANES

a) 2-Amino-4,7-Dimethoxy-5-Methylindane and Related Compounds

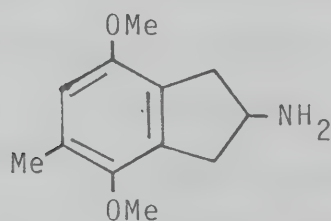
Kang's arguments⁽²⁸⁾ against the pseudo cyclic structures (see page 24) postulated for the psychotomimetic phenethylamines are convincing. The alternative possibility that the amino group of phenethylamines might interact with the receptor by adopting a special conformation such that the amino nitrogen atom would be equivalent to the N-6 atom of LSD is more convincing. The cyclopropyl derivative of mescaline (19) is reported to be an active psychotomimetic agent⁽²¹⁾. In this compound the amino group is fixed and unable to form either of the cyclic structures (21 or 22) thus offering further support to Kang's theory. If a structure closely related to phenethylamine with an amino group fixed in a position similar to the N-6 nitrogen atom of LSD could be synthesized, regardless of whether it was pharmacologically active or not, valuable information could be contributed to the existing structure-activity relationship knowledge of phenethylamine psychotomimetic drugs.

Many derivatives of 2-aminotetrahydronaphthalene have been prepared as analogs of LSD⁽¹³¹⁾. In these compounds, however, the amino group is not completely rigid and can adopt several positions in space, thus making it unsuitable as a model compound. More closely associated with the desired model is 2-aminoindane. Not only is the five

membered ring relatively rigid, as shown in studies of molecular models, but the structure is, in fact, the cyclic analog of α -methylphenethylamine. Molecular models have shown that the amino group is fixed out of the plane of the ring. Although the nitrogen atom in the cyclic structure is not positioned exactly as the N-6 in LSD, it is fixed in a relatively similar position. In addition, the structure would not be capable of forming A/B and A/C conformations reminiscent of LSD (see page 20) as described by Snyder and Richelson⁽²⁴⁾.

A survey of the literature (see introduction) showed that many aminoindanes had been prepared and tested pharmacologically though none of them were reported to possess psychotomimetic properties. Some of the compounds were psychoactive and others had properties in common with LSD; 2-aminoindane, for example, is a potent analgesic⁽¹¹⁵⁾.

The compound chosen for preparation was the cyclic analog of 1-(2,5-dimethoxy-4-methylphenyl)isopropylamine (DOM), namely 2-amino-4,7-dimethoxy-5-methylindane (141).



(141)

Since DOM is one of the most potent of the α -methylphenyl-amine hallucinogens⁽⁵⁾, it was felt that if any cyclic compound was to be active, this ring substitution pattern would be the most promising.

The preparation of 2-amino-4,7-dimethoxy-6-methylindane by two methods was undertaken. The synthetic pathways are summarized in Schemes 30 and 31.

The immediate precursor of (141) employing these reaction schemes, i.e. 2,5-dimethoxy-4-methylcinnamic acid (142), was prepared employing the Doebner modification of the Knoevenagel reaction⁽¹⁸⁷⁾. This procedure involved treating 2,5-dimethoxy-4-methylbenzaldehyde and malonic acid in piperidine and pyridine. The product of the above reaction was then catalytically hydrogenated to yield 3-(2,5-dimethoxy-4-methylphenyl)propionic acid (143).

The use of phosphorus oxychloride⁽¹³⁴⁾ as a reagent to cyclize the saturated acid (143) to 4,7-dimethoxy-6-methyl-1-indanone was next investigated. The product recovered employing this reagent was not only crude and difficult to purify, but was present in low yield. Hence a more suitable means of preparing 4,7-dimethoxy-6-methyl-1-indanone was investigated.

Koo⁽¹³⁵⁾ has reported that phenylpropionic acids are cyclized to 1-indanones in excellent yields when treated with polyphosphoric acid (PPA). Following the general procedure outlined by Koo, 3-(2,5-dimethoxy-4-methylphenyl)propionic

acid was converted to the 1-indanone (144) in good yield and the product was easily purified.

4,7-Dimethoxy-2-isonitroso-6-methyl-1-indanone (145) was recovered when a solution of 4,7-dimethoxy-6-methyl-1-indanone in ethanol and hydrochloric acid was treated with freshly prepared ethyl nitrite gas⁽¹⁸⁸⁾. Because of the low solubility of the isonitroso compound (145) in ethanol, it crystallized from solution as it was formed, thereby providing a good yield of a relatively pure compound.

Reduction of this isonitrosoindanone was first attempted by hydrogenating it as a suspension in acetic acid containing palladium-charcoal. Hydrogen was rapidly absorbed. When the incorporation of hydrogen ceased, the catalyst and solvent were removed, leaving a red-black oil. After several unsuccessful attempts to isolate a pure product from the oil, it was discarded.

When a suspension of the isonitroso compound (145) in ethanol and hydrochloric acid was similarly hydrogenated, a white water-soluble solid was recovered. An aqueous solution of this solid, when basified, turned a dark red color. An ethanolic solution of the same material slowly turned red during a recrystallization process. This could be prevented by the addition of a small amount of hydrogen chloride gas to the solution. Because these reducing conditions are reported to produce 2-amino-1-indanones as the major products^(124,125,129), and since these compounds

are known to dye objects 'shocking pink' (189), it appeared likely that the compound formed was 2-amino-4,7-dimethoxy-6-methyl-1-indanone hydrochloride (146).

The infrared spectrum of 2-amino-4,7-dimethoxy-6-methyl-1-indanone hydrochloride was consistent with its structure. In addition to absorption bands characteristic of the primary amine salt, a strong carbonyl stretching frequency at 1720 cm^{-1} was present in the spectrum. Present in the nmr spectrum were one 1-proton aromatic signal and three 3-proton methyl signals (i.e. the 4- and 7- OCH_3 groups and the 6-methyl group) as well as broad 2-proton and 1-proton signals. Also present in the spectrum was a broad 3-proton signal which exchanged with deuterium oxide. The compound, however, analyzed incorrectly for 2-amino-4,7-dimethoxy-6-methyl-1-indanone hydrochloride. Because it was very difficult to crystallize to a sharp melting product, it was assumed to be impure.

The reduction of 2-amino-1-indanone with sodium borohydride is reported (137) to yield trans-2-amino-1-indanol. When 2-amino-4,7-dimethoxy-6-methyl-1-indanone was reduced with this reagent, a white basic solid material which melted at a temperature different from that of the starting material was recovered. The infrared spectrum of its hydrochloride salt displayed an OH stretching absorption band at 3350 cm^{-1} ; a carbonyl peak at 1720 cm^{-1} was absent. The mass spectrum as well as elemental analysis data agreed

with the structure being 2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride (147).

2-Amino-1-indanols have been recovered following the hydrogenation of a solution of the corresponding 2-isonitroso-1-indanone in ethanolic sodium hydroxide containing Raney nickel^(111,128,130). 2-Isonitroso-4,7-dimethoxy-6-methyl-1-indanone was reduced under conditions similar to those reported, except that palladium-charcoal was used as the catalyst. The product recovered from the reaction was identical with 2-amino-4,7-dimethoxy-6-methyl-1-indanol.

Since 2-amino-1-indanols and 2-amino-1-tetralols undergo a rearrangement to form 2-indanones and tetralones when treated with acids^(126,137-139) the preparation of 4,7-dimethoxy-5-methyl-2-indanone (148) was attempted using these conditions. After heating a solution of 2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride in hydrochloric acid, a yellow solid separated from the solution; it was collected. The filtrate was heated further and more solid formed. This procedure was repeated until the formation of solid ceased.

The infrared spectrum of this product was devoid of absorbances characteristic of primary amines but displayed a strong absorbance peak at 1750 cm^{-1} . A red precipitate formed when a solution of the material was treated with 2,4-DNP reagent. This data strongly suggested that the material was a ketone. Since the carbonyl group of 2-inda-

nones is reported⁽¹⁹⁰⁾ to absorb near 1750 cm^{-1} , it appeared that the unknown possessed structure (148). The nmr spectrum of this material was also in agreement with the 2-indanone structure. Present in the spectrum were three 3-proton singlets (i.e. the 4- and 7- OCH_3 and the 5-methyl group), 1-proton aromatic signal, and two 2-proton methylene signals. The molecular ion in its mass spectrum was present at m/e 206; this corresponds to the molecular weight of the 2-indanone (148). The compound, however, analyzed indifferently for structure (148). In view of the convincing spectral evidence, it would appear that the compound is 2-indanone (148) but is not pure.

The oxime of 4,7-dimethoxy-5-methyl-2-indanone (149) was then synthesized by treating (148) with hydroxylamine. Although the oxime was easily prepared, its reduction to the 2-aminoindane (141) was not as simple as anticipated. When an ethanol solution of the oxime (149) was hydrogenated in the presence of palladium-charcoal or platinum dioxide, no hydrogen was incorporated and starting material was recovered. The same hydrogenation was repeated, except that the reaction time was considerably extended. When the solution was saturated with gaseous hydrogen bromide and the solvent removed, a dark brown oil was obtained. Attempts to isolate any pure material from the oil failed.

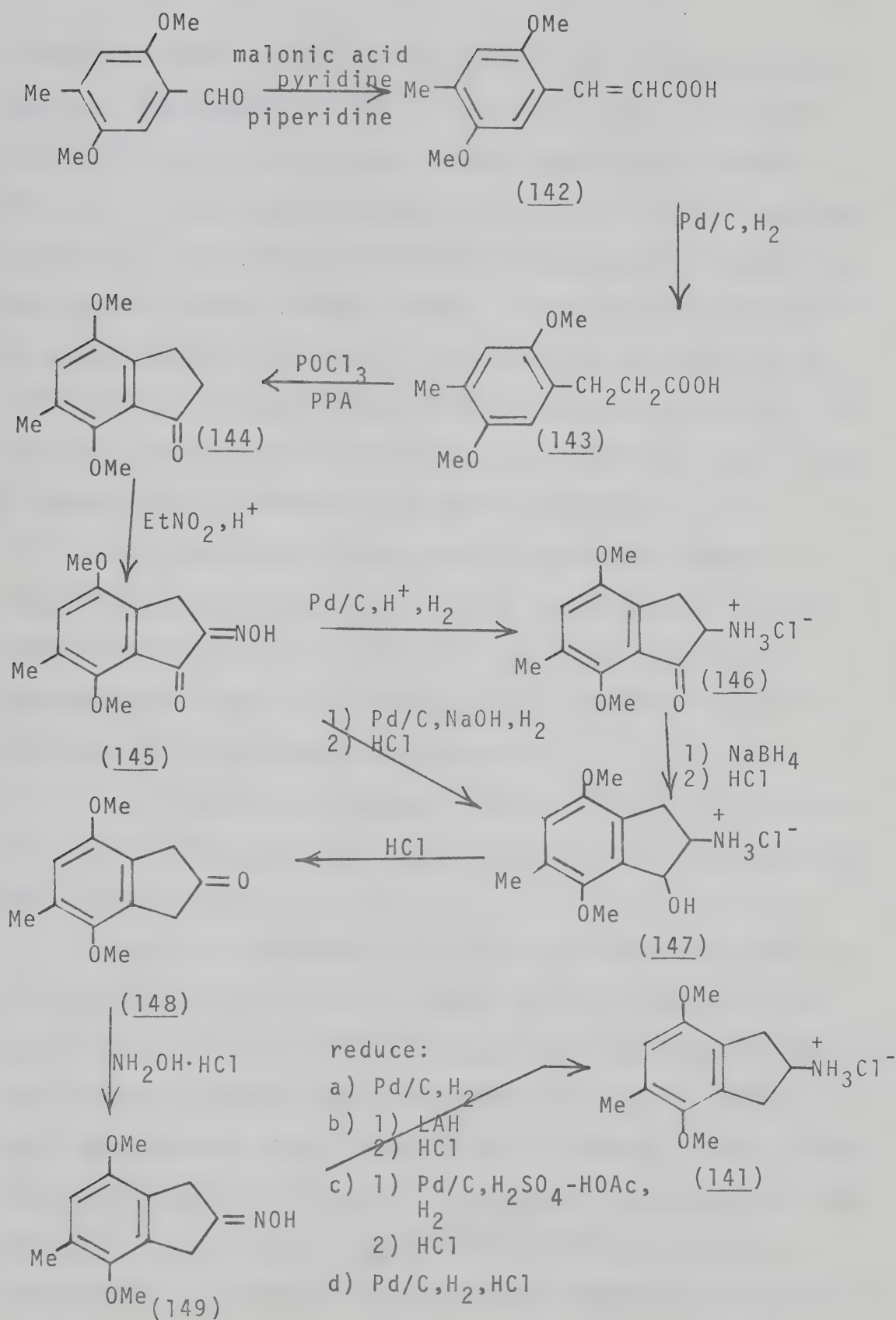
Since the oxime of 2-indanone has been reduced to 2-aminoindane in 45% yield⁽¹⁹¹⁾ with lithium aluminum

hydride, a lithium aluminum hydride reduction of (149) was undertaken. Because this oxime was virtually insoluble in ether and tetrahydrofuran, a fine suspension of it in ether was added to a suspension of lithium aluminum hydride in the same solvent. The reaction was then heated under reflux for two days. The amount of basic material recovered from the reaction was very low. It was characterized by means of its infrared spectrum which showed that the material was a primary amine salt. Since the quantity of this material was small, further attempts to isolate more of the material by another route were undertaken.

A more exhaustive literature survey revealed that oximes of 2-indanones are very difficult to reduce. Various reductive methods including sodium amalgam⁽¹⁹²⁾, sodium and alcohol⁽¹⁹³⁾, platinum black and hydrogen⁽¹⁹³⁾, platinum dioxide and hydrogen⁽¹⁸⁸⁾, ferrous sulfate⁽¹⁸⁹⁾, zinc and acetic acid⁽¹⁹⁴⁾, sodium borohydride with or without palladium-charcoal⁽¹⁹⁵⁾, and palladium-charcoal catalyzed hydrogenation in ethanol containing hydrochloric acid^(189, 119) had largely proved to be unsuccessful.

Levin⁽¹¹⁹⁾ used activated palladium catalysts to reduce the oxime of 2-indanone and isolated excellent yields of the 2-aminoindane. The catalysts they used were reported to be very active, sensitive, and pyrophoric.

Rosen and Green⁽¹⁸⁹⁾ undertook a detailed study of the reduction of the oxime of 2-indanone. They were able



Scheme 30

to obtain yields of 2-aminoindane as high as 93% by hydrogenating the oxime in acetic acid containing a 2.2 molar ratio of sulfuric acid and a large amount of palladium-charcoal. When the reduction of the oxime of 4,7-dimethoxy-5-methyl-2-indanone was undertaken employing the conditions described by these latter workers, a product was isolated in approximately 50% yield. The infrared spectrum of the corresponding hydrochloride salt was superimposable on the infrared spectrum of the material isolated from the lithium aluminum hydride reduction of the same oxime.

The reduction of the oxime (149) with hydrogen in ethanolic hydrochloric acid containing palladium-charcoal (these conditions were reported to be unsuccessful in reducing the oxime of 2-indanone⁽¹⁸⁹⁾) afforded 2-amino-4,7-dimethoxy-5-methylindane in 30% yield.

The alternative synthetic route (Scheme 31) in which the 2-amino-1-indanol was reduced to the 2-aminoindane was next investigated.

Since the aminoindanol (147) is a secondary benzylic alcohol, it was felt that it would readily form cis- and trans-2-amino-1-chloro-4,7-dimethoxy-6-methylindane (150) and possibly the enamine (151) in hydrochloric acid. Since these derivatives might be expected to reduce to the corresponding hydrocarbon (141) in the presence of a catalyst and hydrogen, a solution of the 2-amino-1-indanol (147) in hydrochloric acid under these reducing conditions should

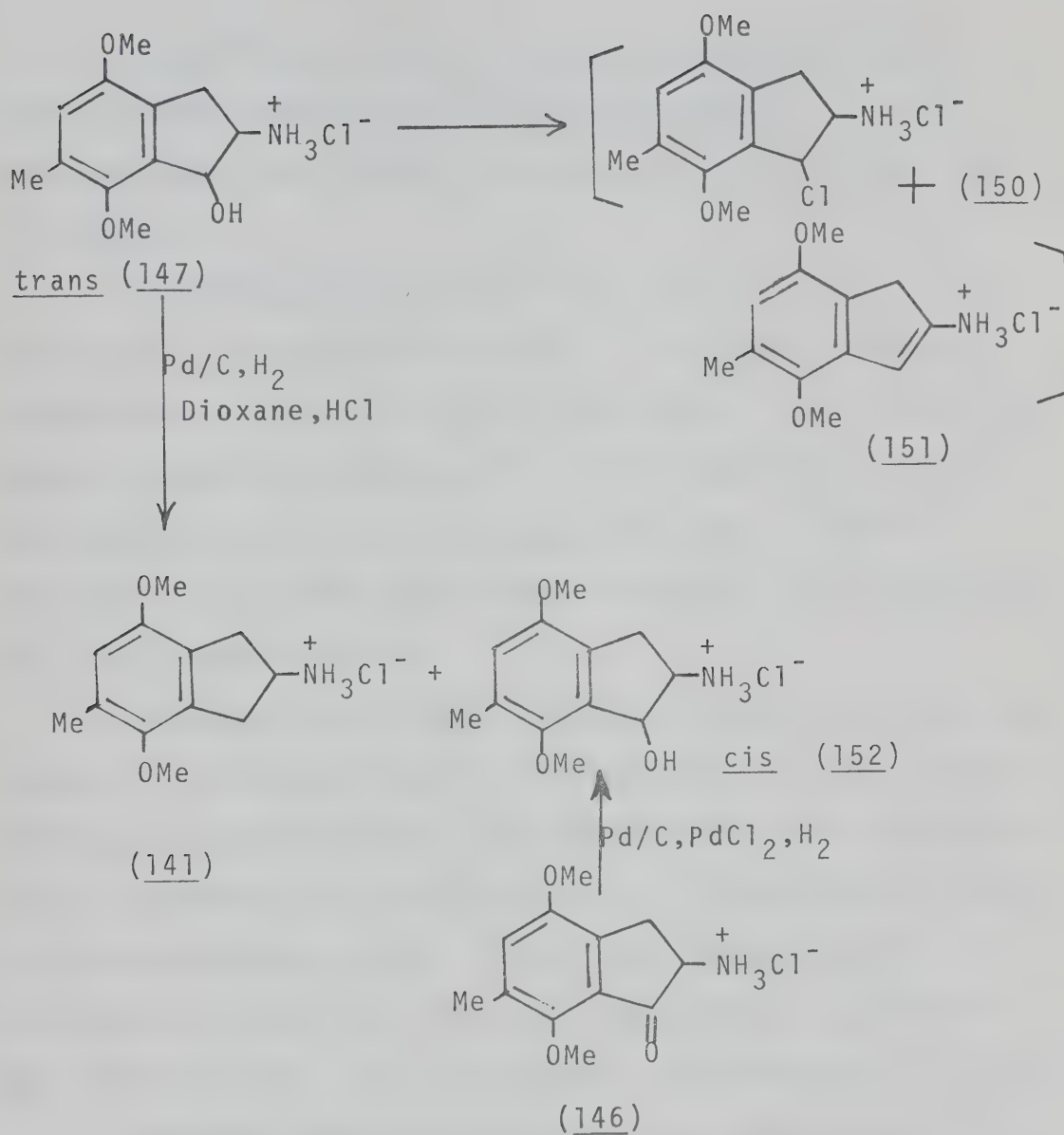
result in the formation of 2-amino-4,7-dimethoxy-5-methylindane. These postulated reactions are summarized in Scheme 31. An advantage of this procedure over a method employing a solvent consisting of acetic acid and sulfuric acid^(118,121) is that hydrochloric acid can be removed by evaporation on completion of the reduction, thereby leaving the hydrochloride salt of the 2-aminoindane as the product.

After experimenting with several reaction conditions, a suitable procedure was found. The aminoalcohol (147) was dissolved in a solvent consisting of equal volumes of hydrochloric acid and dioxane, then hydrogenated at room temperature and atmospheric pressure in the presence of palladium-charcoal. A reasonable yield of 2-amino-4,7-dimethoxy-5-methylindane was recovered from the reaction. A second product (152) which melted at a temperature different from that of the starting aminoindanol (147) or the 2-aminoindane (141) was also isolated. The infrared spectrum of this unknown compound displayed an OH stretching band near 3150 cm^{-1} ; this differs from the starting aminoindanol which had an OH stretching absorption near 3350 cm^{-1} . It, however, had an elemental analysis which corresponded to 2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride. The molecular ion in its mass spectrum was present at m/e 233, thereby confirming that it was the isomeric cis-2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride.

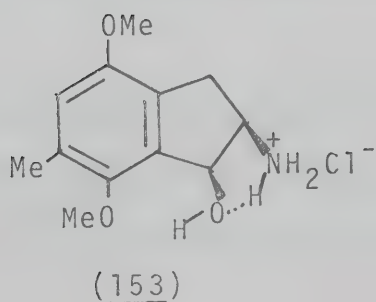
Examination of the molecular model of the cis-form of

2-amino-1-indanol showed that a 5-membered intramolecularly bonded ring as shown by structure (153) could be formed. Since such a structure is not possible in the trans-isomer, this could explain the absorption of the OH group in the infrared spectrum of the cis-isomer near 3150 cm^{-1} .

To verify that the second product was in fact the cis-2-amino-1-indanol (152), a stereospecific reduction of 2-amino-4,7-dimethoxy-6-methyl-1-indanone to the cis-2-amino-1-indanol was undertaken. This reduction involved hydrogenation of the aminoindanone (146) in the presence of palladium-charcoal and palladium chloride^(127,129). The product isolated from the reaction was identical with what was deduced above to be the cis-isomer. Therefore, when a solution of trans-2-amino-4,7-dimethoxy-6-methyl-1-indanol in hydrochloric acid was hydrogenated in the presence of palladium-charcoal, two reactions, reduction and isomerization, were occurring. Isomerization could also have occurred during the process of removal of the solvent. This, in fact, seemed more likely since cis-2-amino-4,7-dimethoxy-6-methyl-1-indanol was recovered following treatment of the corresponding trans-isomer (147) with concentrated hydrochloric acid. The cis-isomer (152) increased in concentration with increasing solution time. The same solution, if heated on a water bath for short periods of time, yielded the cis-isomer as the major product, while a small amount of the 2-indanone (148) was also produced.



Scheme 31



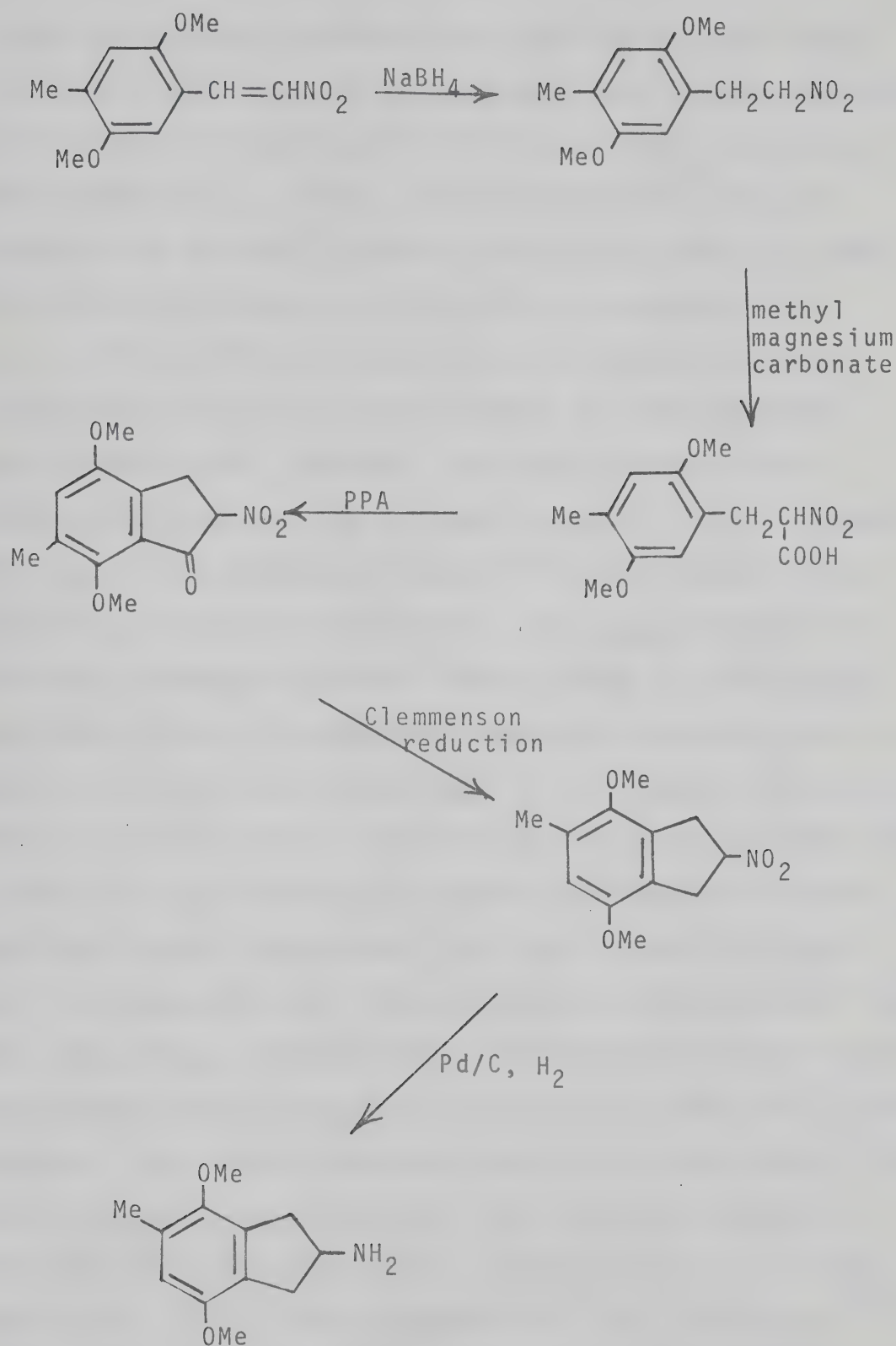
In addition to the two methods just described to prepare 2-amino-4,7-dimethoxy-5-methylindane, a third possible route was briefly investigated and is summarized in Scheme 32.

The carboxylation step⁽¹⁹⁶⁾ in Scheme 32 was unsuccessful, the failure probably being due to improper preparation of magnesium methyl carbonate. Absolutely dry carbon dioxide is necessary for the preparation, but the only grade available was not completely dry. Because of the delay in obtaining dry carbon dioxide, this scheme was not investigated further.

Although the 2-amino-1-indanols (147) and (152) were prepared as intermediates in the synthesis of 2-amino-4,7-dimethoxy-5-methylindane, their pharmacological evaluation might contribute to structure-activity relationship studies of psychotomimetic drugs. Since these aminoindanols are structurally similar to the neurotransmitters, adrenaline and noradrenaline, they may possess some adrenergic activity.

Although these compounds were not thoroughly evaluated pharmacologically, one can theorize with reference to the known structure-activity relationships of hallucinogens what the effects of the 1-OH group might be on psychotomimetic activity.

If 2-amino-4,7-dimethoxy-5-methylindane, DOM, and LSD all interact with the same theoretical receptor and the amines of the indane (141), and DOM binds to the same site



Scheme 32

as the N-6 nitrogen atom of LSD, then the availability of the binding electrons on the nitrogen atom becomes important. Only one of the two isomers of LSD has potent psychotomimetic properties. It has been postulated⁽²⁸⁾ that the electrons on the N-6 nitrogen atom of the inactive isomer of LSD are not available to bind with the receptor.

The binding electrons on the nitrogen atoms of 2-amino-4,7-dimethoxy-5-methylindane and DOM should be equally available. However, the availability of the binding electrons on the nitrogen atoms of the two isomers of 2-amino-4,7-dimethoxy-6-methyl-1-indanol would not be expected to be equally available. In trans-2-amino-4,7-dimethoxy-6-methyl-1-indanol the OH group is fixed above the plane of the five-membered ring and the amino group is held below the plane. Therefore the electrons of the amine should be as available as the electrons on the nitrogen atom of DOM. In cis-2-amino-4,7-dimethoxy-6-methyl-1-indanol both the OH and amino groups are fixed below the plane of the five-membered ring. The electrons on the nitrogen atom are less likely to be available to interact with the receptor because the OH group could sterically hinder the close binding. The binding electrons on the nitrogen atom of this isomer would be expected to be less available because, in addition, they are involved in the formation of an intramolecularly bonded five-membered ring (153) described previously. Therefore, if both the cis- and trans-amino-

alcohols (147), (152) can reach the receptor with equal ease, the trans-amino alcohol (147) would be expected to be the more active isomer.

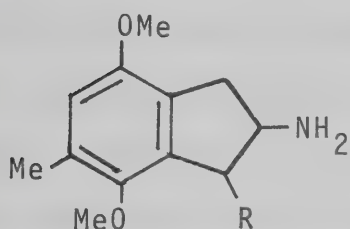
Structure-activity relationship studies on the psychotomimetic phenethylamines have shown that the activity of this class of compounds is maximal when there is an α -methyl branch⁽¹⁰⁾. Increasing the α -branch beyond a methyl group results in a decrease in activity. Although this relationship has not been explained, it is possible that increasing the size of the α -group sterically impedes binding of the nitrogen atom onto the theoretical receptor. If DOM and 2-amino-4,7-dimethoxy-5-methylindane both attach to the same receptor, then, on the basis of the structure-activity studies of the phenylisopropylamines, any substitution on the 1-position of the former compound would be expected to result in a decrease of psychotomimetic activity. For this reason both the cis- and trans-aminoindanols (147) and (152) may be inactive.

A preliminary pharmacological screening of 2-amino-4,7-dimethoxy-6-methylindane in rats revealed that it had CNS activity much like DOM.

b) The Preparation and Properties of Some 2-Amino-4,7-dimethoxy-6-methyl-1-substituted Indanes

The synthesis of 1-substituted-2-aminoindanes (150), (154a - 154c) was next undertaken. A pharmacological evaluation of these structures, as well as the cis-and

trans-aminoalcohols (147) and (152), would provide information on what effect substitution at the 1-position of 2-aminoindanes has on activity relative to the parent 2-aminoindane (141).



R = OMe (154a)

R = OEt (154b)

R = OPr (154c)

R = Cl (150)

Structures (154a - 154c) were chosen for this study because they were considered to be easily synthesized, and their pharmacological evaluation would provide some insight into the effects that varying the size of the group at the 1-position of 2-aminoindanes would have on activity.

Compound (150) is not only an interesting structure because it resembles 2-amino-4,7-dimethoxy-6-methylindane, but it could conceivably be converted under biological conditions to the corresponding enamine (151) which has not been reported in the literature.

The preparation of compounds (154a - 154c) was deemed possible by employing the route summarized in Scheme 33.

If a solution of 2-amino-4,7-dimethoxy-6-methyl-1-indanol in the appropriate alcohol and hydrochloric acid was heated, the OH group of the aminoindanol would be

expected to be protonated by the acid, thereby resulting in the expulsion of water and the formation of the 1-chloro derivative (150). Since the chloro group is also a good leaving group, it is feasible that this compound could then undergo a nucleophilic substitution reaction with the alcohol or water, thereby forming the corresponding cis- and trans-aminoalcohols (147) and (152) and ethers (154a - 154c). Although water is a stronger base than the alcohol, its concentration is low relative to the alcohol; therefore a substantial amount of the ether should be formed.

The synthesis of 2-amino-1,4,7-trimethoxy-6-methylindane (154a) was attempted by heating a solution of trans-2-amino-4,7-dimethoxy-6-methyl-1-indanol in anhydrous methanol and hydrochloric acid. After the solution was heated under reflux for two hours, the solvent was removed. The absence of an orange precipitate when the crude residue was treated with 2,4-DNP reagent indicated that no 2-indanones (148) had formed under these conditions. Only starting material was recovered. The reaction was then repeated; however, the reaction time was extended to 15 hours. In addition to cis-2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride, a solid melting at a temperature near that of the former compound, was isolated from the reaction mixture. Mixed melting point determinations as well as infrared spectral comparisons revealed that the product was different from the starting material or its

cis-isomer (152). Because the OH absorption band was absent and a band near 1170 cm^{-1} (characteristic of an aliphatic ether) was present in the infrared spectrum, it appeared that the compound was the desired methyl ether (154a). It, however, had an elemental analysis different from the calculated values for structure (154a). In an attempt to identify this material, a nmr spectrum as well as mass spectrum were recorded and examined.

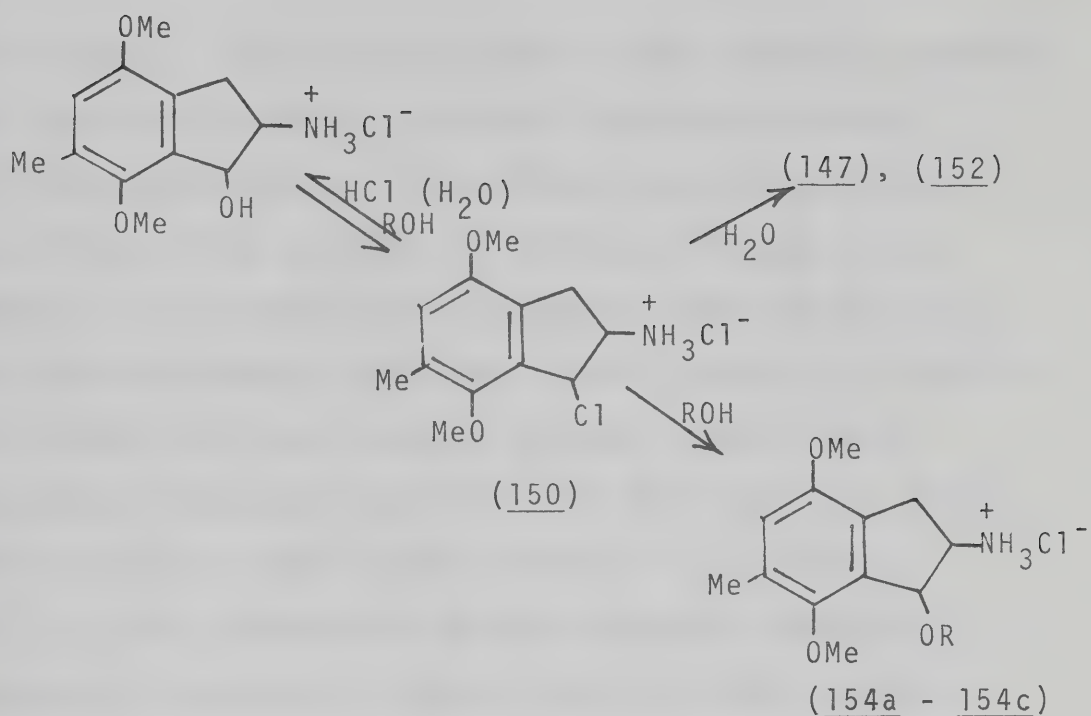
Present in the nmr spectrum, recorded in deuterium oxide, were: a 9-proton singlet, a 6-proton singlet (OCH_3 protons), a 1-proton aromatic signal, a 1-proton doublet, a 2-proton triplet, and a 1-proton multiplet.

The molecular ion in the mass spectrum was present at m/e 263. This then fragmented with the loss of 15 a.m.u.

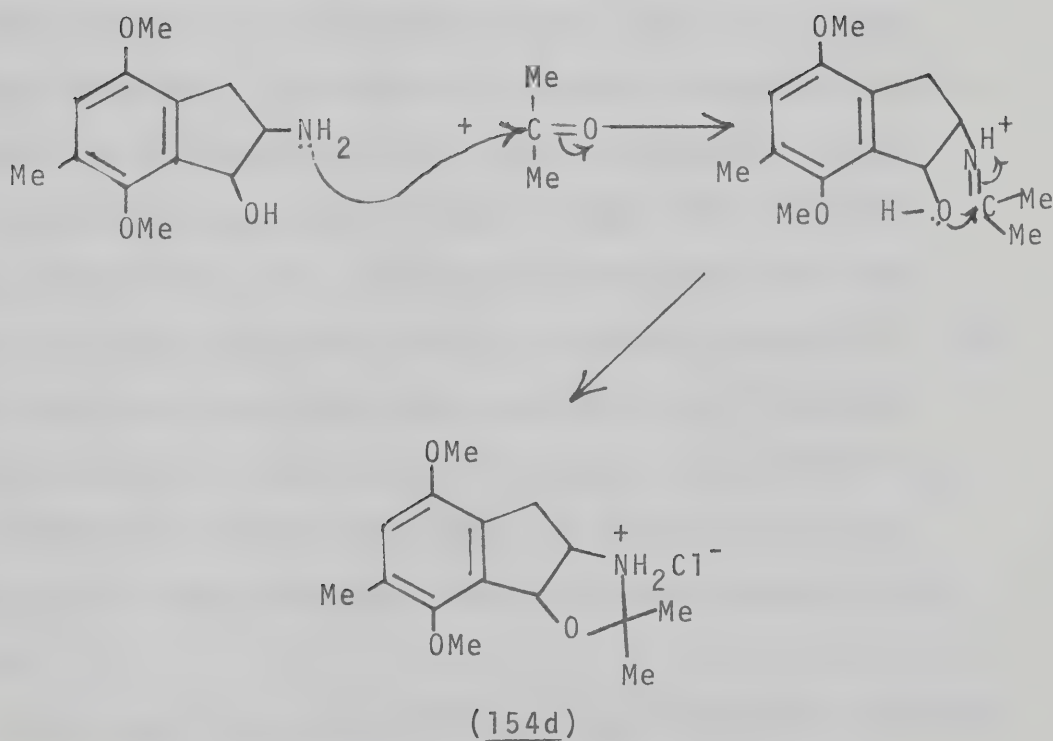
These spectral data fit the compound shown by structure (154d). Not only does it have the correct number of protons in the nmr spectrum, it would be expected to readily lose a CH_3 radical on electron impact. Its elemental analysis was also consistent with structure (154a).

Since acetone was used in the 'workup' procedure, it is likely that structure (154d) was formed by the route shown in Scheme 33a.

The preparation of the ethyl ether derivative (154b) was undertaken by heating a solution of trans-2-amino-4,7-dimethoxy-1-indanol hydrochloride in ethanol and hydro-



Scheme 33



Scheme 33a

chloric acid. The use of acetone in the 'workup' procedure was, however, avoided. The crude residue recovered following evaporation of the solvent was fractionally crystallized from ethanol and ether. Although it was difficult to separate pure components from the mixture, the cis-aminoindanol (152) and a small quantity of another solid whose infrared spectrum did not display an OH absorbance band were isolated. The molecular ion in the mass spectrum of this latter compound was present at m/e 251; this corresponds to the molecular weight of 2-amino-4,7-dimethoxy-1-ethoxy-6-methylindane (154b). Because of the small amount of product recovered, its elemental analysis was not determined, nor was its nmr spectrum recorded. Therefore it is only assumed that this material was the desired ethyl ether derivative (154b)

When the trans-aminoindanol (147) was similarly heated under reflux in a solvent of propanol and hydrochloric acid for 15 hours, only a very small amount of the propyl ether analog (154c) was recovered by fractional crystallization of the reaction product. This material was assigned the structure (154c) on the basis of the appearance of the molecular ion in the mass spectrum at m/e 265.

Although the crude mixture of each reaction was not completely separated, it appeared that a variety of compounds were present; this procedure was therefore

considered a poor synthetic route. Modifications of the reaction conditions could increase the yield of the ethers, but such modifications were not investigated. Sufficient quantities of the ethyl ether analog were obtained to permit a preliminary screening to determine whether such modifications were warranted.

This compound failed to induce effects in rats similar to those observed with DOM, hence further work in this direction was discontinued.

Since 2-amino-1-chloro-4,7-dimethoxy-6-methylindane hydrochloride (150) was postulated to be an intermediate in the formation of compounds (141) and (152), the procedure used to prepare this material simply involved stirring a solution of the trans-2-amino-1-indanol hydrochloride in concentrated hydrochloric acid. The products isolated from the reactions were the cis- and trans-2-amino-1-indanols (147) and (152) and a small quantity of a third compound. This compound analyzed indifferently for $C_{12}H_{17}Cl_2NO_2$ and unexplainable bands between 3000 and 3500 cm^{-1} in its infrared spectrum indicated that it was impure or not structure (150). Nevertheless, the molecular ion in the mass spectrum of this material was located at m/e 241; a second ion was present at m/e 243. Since the abundance of the former ion was approximately three times that of the latter, the presence of a covalently bonded chlorine atom was indicated. This observation was

consistent with the product being 2-amino-1-chloro-4,7-dimethoxy-6-methylindane.

In an attempt to increase the yield of (150), the mixture of cis- and trans-aminoindanols (147) and (152) was gently heated with concentrated hydrochloric acid. This treatment resulted only in an increased formation of the cis-isomer (152).

An alternative synthetic route of preparing the 1-chloro analog (150) was undertaken. This involved the reaction of trans-2-amino-4,7-dimethoxy-6-methyl-1-indanol with thionyl chloride. This method proved unsuccessful and further attempts to prepare this analog were not undertaken.

c) Derivatives of Amino-4,7-dimethoxy-6-methylindanes

Although the amino group of 2-aminoindanes is fixed in a position somewhat equivalent to the N-6 nitrogen atom of LSD, and hence could interact with the same sites on a hypothetical receptor as the aromatic ring and the N-6 nitrogen atom of LSD, the degree of interaction with the receptor may not occur to the same extent as LSD. This is understandable since the N-6 nitrogen atom of LSD is tertiary and hence more basic than the primary amino group of the 2-aminoindane. Therefore the synthesis of compounds in which the basicity of the 2-amino group was similar to the tertiary amino group of LSD was undertaken.

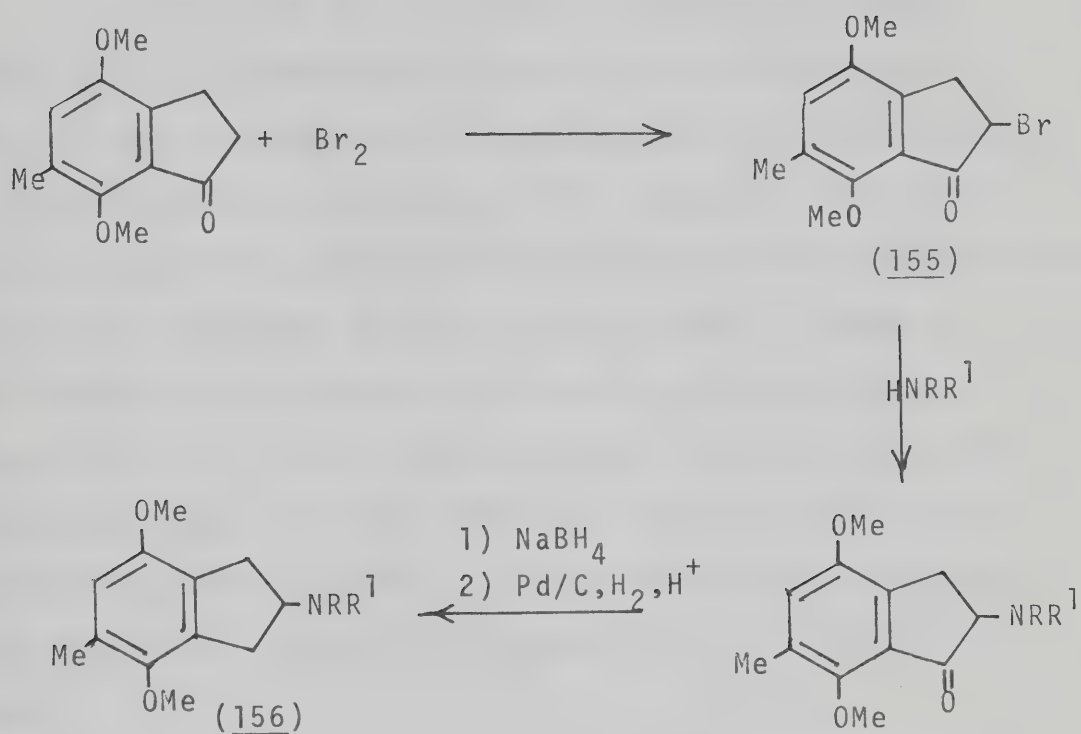
A synthesis of compounds of general structure (156)

where R and R¹ were alkyl groups was envisaged by employing the method summarized in Scheme 34. However, the bromination reaction⁽¹⁹⁷⁾ was unsuccessful and no 2-bromo-1-indanone (155) was recovered from the black, tarry reaction product.

The synthesis of a specific compound of general structure (156), namely 4,7-dimethoxy-2-dimethylamino-5-methylindane (156a) was then investigated. The preparation of this compound involved subjecting an aqueous solution of 2-amino-4,7-dimethoxy-5-methylindane hydrochloride and a slight excess of formaldehyde to hydrogenation in the presence of palladium-charcoal⁽¹⁹⁸⁾. A poor yield of a compound was recovered from the reaction. The infrared spectrum of this material displayed bands characteristic of a tertiary amine salt and the position of the molecular ion in its mass spectrum was consistent with structure (156a).

The amino group of (156a) is not only tertiary and hence as basic as the N-6 atom of LSD, but it is also free to rotate and therefore can adopt a conformation such that the two methyl groups correspond to the two substituents on the N-6 nitrogen atom of LSD. Since the methyl groups are relatively small, the nitrogen atom of (156a) could be as accessible to the receptor as the N-6 nitrogen atom of LSD.

The dimethylamino analogs (157a) and (157b) were

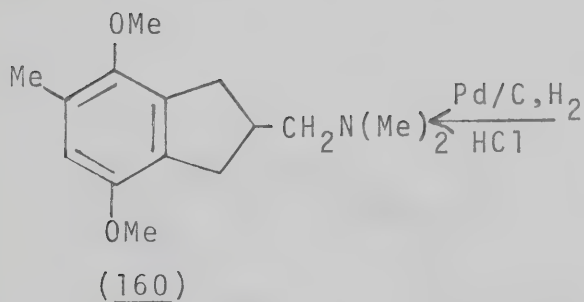
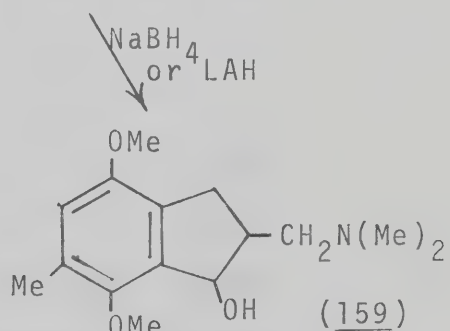
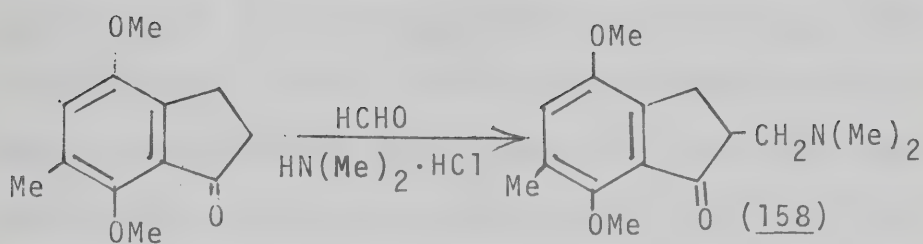
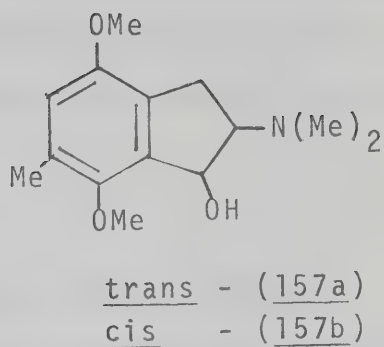
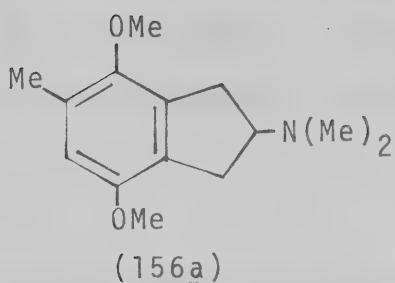


Scheme 34

also prepared from (147) and (152) respectively by using the same reductive methylation procedure and were characterized by means of their elemental analyses and mass spectra. The yields of both products were relatively low.

A homolog of the 2-amino-4,7-dimethoxy-5-methylindane was also prepared so that the positional requirements of the nitrogen atom of phenethylamine psychotomimetic drugs might be determined. The compound was 4,7-dimethoxy-5-methyl-2-(dimethylamino)methylindane hydrochloride (160), the synthesis of which is outlined in Scheme 35. It was reasoned that although this amine was not a primary amine like the 1- and 2-aminoindanes, its pharmacological evaluation could indicate whether or not further investigations into the synthesis of compounds related to (160) were warranted. Like LSD, compound (160) is a tertiary amine.

The Mannich reaction, in which 4,7-dimethoxy-6-methyl-1-indanone was treated with formaldehyde and dimethylamine hydrochloride⁽¹⁹⁹⁾, was used to prepare 4,7-dimethoxy-6-methyl-2-(dimethylamino)methyl-1-indanone (158). The corresponding indanol (159) was then prepared by reducing the indanone (158) with either lithium aluminum hydride or sodium borohydride. The reduction employing the latter reagent proved to be much more successful than the same reduction with the former reagent. The indanol (159) was then hydrogenated in a solvent of equal



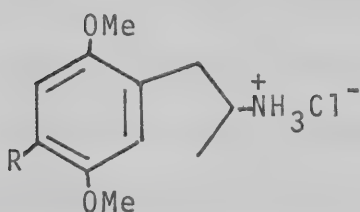
Scheme 35

parts of dioxane and hydrochloric acid under palladium-charcoal to yield (160). The products isolated were characterized by elemental analysis and infrared spectral data.

d) The Synthesis of Miscellaneous 2-Aminoindanes

Preliminary pharmacological screening of 2-amino-4,7-dimethoxy-6-methylindane hydrochloride in rats revealed that it had CNS activity much like DOM, and hence the preparation of additional 2-aminoindanes was undertaken.

Since 2-(4-substituted-2,5-dimethoxyphenyl)isopropylamines (10e - 10i) appeared to be psychoactive agents, the synthesis of the corresponding analogs (161a - 161f) were investigated. It was felt that a pharmacological comparative study of these two classes of compounds might assist in determining whether phenethylamines and their cyclic analogs share a common receptor.



R = H (10f)

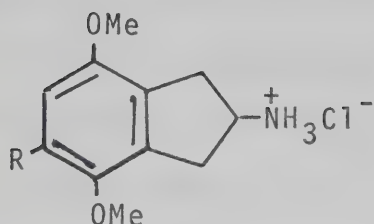
R = Cl (10g)

R = Br (10e)

R = I (10h)

R = NO₂ (10i)

R = NH₂ (10j)



R = H (161a)

R = Cl (161b)

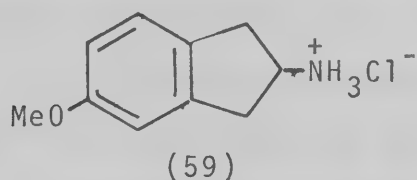
R = Br (161c)

R = I (161d)

R = NH₂ (161e)

R = NO₂ (161f)

An investigation of another 2-aminoindane, namely 2-amino-5-methoxyindane (59), was also undertaken. This structure is the cyclic analog of the known hallucinogen 1-(4-methoxyphenyl)isopropylamine.



The first attempt to prepare compounds (161b - 161f) required the preparation of the aminoindanone (169). It was reasoned that once this material was obtained, it could be subjected to the Sandmeyer reaction to yield the indanones (170a - 170c). These structures could then be treated as described for the synthesis of 2-amino-4,7-dimethoxy-5-methylindane to yield the desired compounds (161b - 161f). These reactions are summarized in Scheme 36.

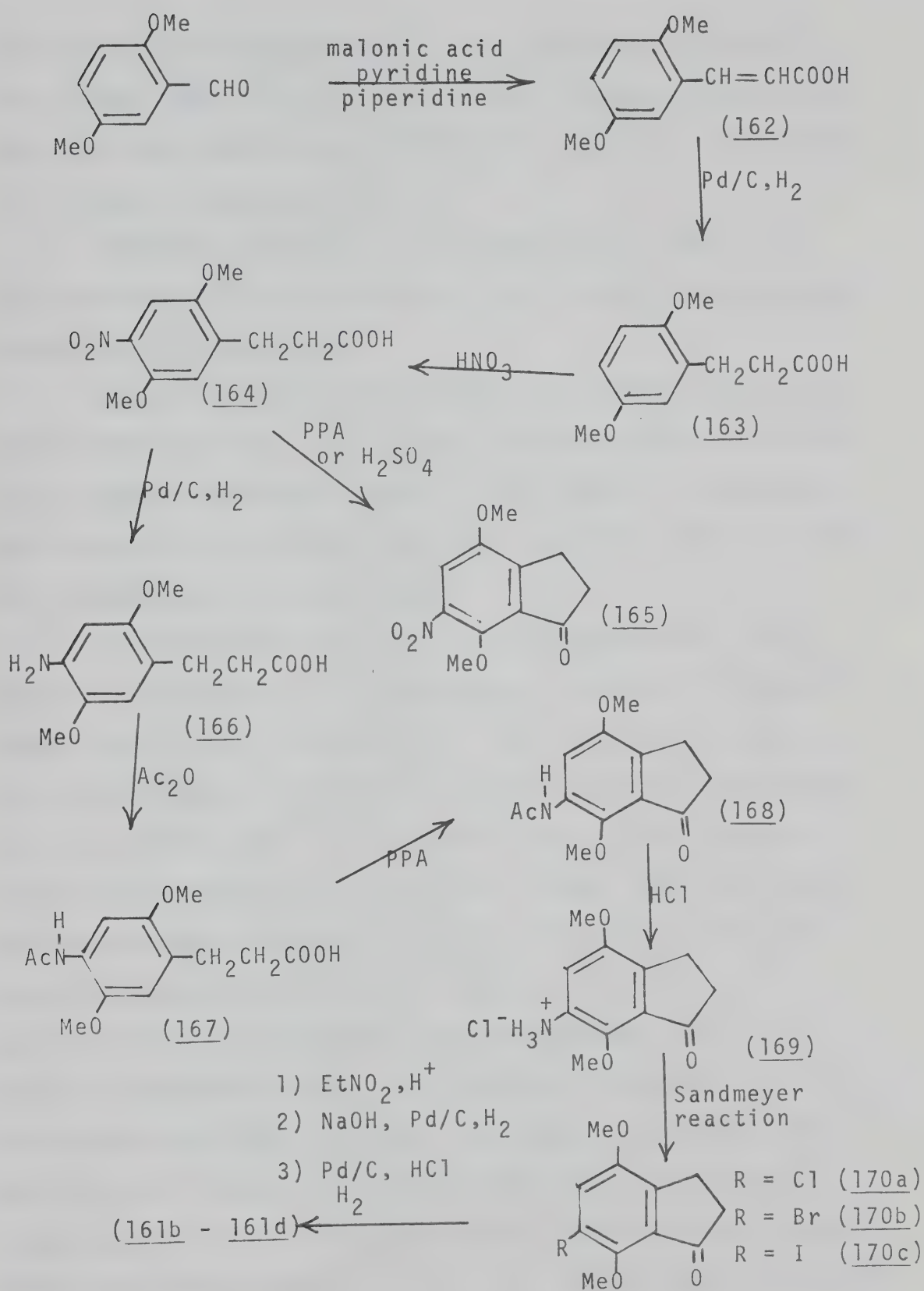
2,5-Dimethoxycinnamic acid (162) was prepared by condensing 2,5-dimethoxybenzaldehyde and malonic acid.

The product was then catalytically hydrogenated to 3-(2,5-dimethoxyphenyl)propionic acid (163).

3-(2,5-Dimethoxy-4-nitrophenyl)propionic acid (164) was obtained when 3-(2,5-dimethoxyphenyl)propionic acid was treated with nitric acid⁽¹⁴³⁾. The elemental analysis of the product recovered from the reaction corresponded to a mono-nitrated derivative of (163). Two 1-proton singlets appeared in the aromatic region of the nmr spectrum of this material. This confirmed that the substitution of the nitro group occurred at the 4-position of the phenyl ring.

The preparation of 4,7-dimethoxy-6-nitro-1-indanone (165) was then attempted by cyclizing 3-(2,5-dimethoxy-4-nitrophenyl)propionic acid with polyphosphoric or sulfuric acid. Both of these procedures proved unsuccessful. This failure may have resulted from the deactivation of the aromatic ring by the electronegative nitro group. An alternative method of preparing (169) was then investigated.

Since the acetamido group is not a ring deactivating group, and since it is the precursor to an amine, the preparation of 3-(4-acetamido-2,5-dimethoxyphenyl)propionic acid (167) was undertaken in view of the fact that this compound could be converted to (169) by the series of reactions shown in Scheme 36. A palladium-charcoal catalyzed reduction of the nitro-compound (164) gave the amine (166) which was treated with acetic anhydride to produce the acetamide (167). When this acetylated amino acid was



Scheme 36

subjected to the polyphosphoric acid cyclization reaction, only a very poor yield of the indanone (168) was recovered. The acid environment was sufficient to hydrolyze the amide before cyclization was effected.

Hydrolysis of (167) to the amphoteric amino acid (166) probably also occurred when cyclization was attempted employing sulfuric acid.

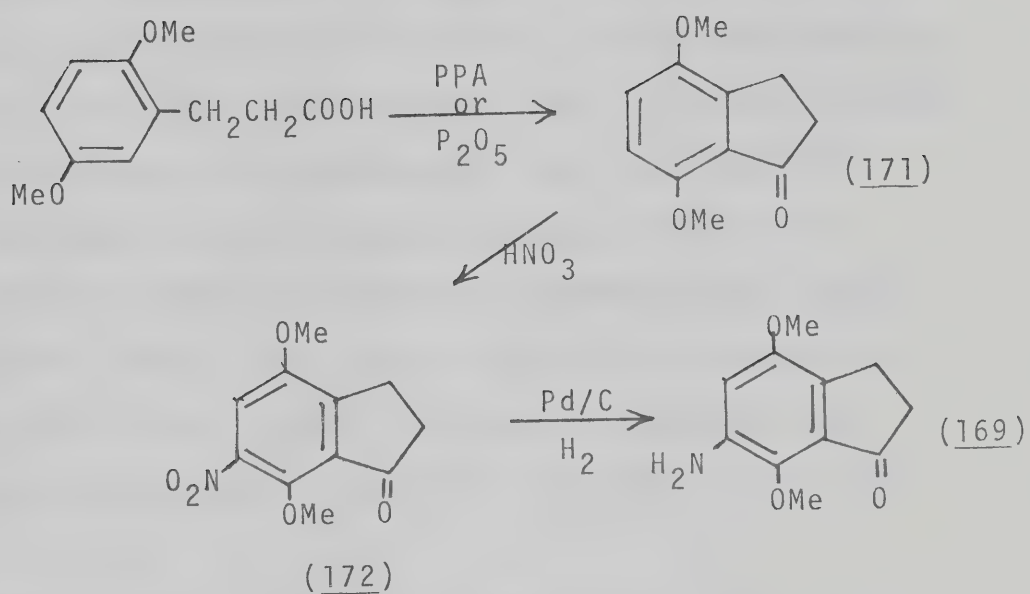
When 6-acetamido-4,7-dimethoxy-1-indanone was heated in hydrochloric acid, the product isolated was the desired amine (169). The final yield of this product, employing the sequence of reactions described, was very low, and hence this synthesis was discontinued.

The procedure next employed to prepare the amine (169) was nitration of 4,7-dimethoxy-1-indanone followed by reduction as shown in Scheme 37. When the cyclization of 3-(2,5-dimethoxyphenyl)propionic acid (163) was undertaken as described by Koo⁽¹³⁵⁾, the isolation of the indanone (171) was not easily accomplished. After (163) was heated with polyphosphoric acid for various lengths of time, the reaction mixture was poured in water. A dark red oil separated and was extracted into chloroform. Since the infrared spectrum of the crude product displayed a strong absorbance band near 1710 cm^{-1} and gave a positive test with 2,4-DNP reagent, it was apparent that some indanone (171) was present. In an attempt to separate this indanone from uncyclized acid (163), the crude mixture was dissolved

in chloroform, then extracted with a sodium bicarbonate solution. However, a very thick stable emulsion developed upon shaking the mixture. Even after standing for two weeks the emulsion had not completely cracked. Similar emulsions resulted when benzene was the solvent. When ether was employed, the emulsion which formed was found to be less stable. Generally, cooling or adding brine to the emulsion did not hasten its separation. Substituting a 5% sodium carbonate solution in place of sodium bicarbonate proved more satisfactory because less stable emulsions developed. It was also generally observed that when working on a large scale, yields were lower and greater difficulties were experienced in the isolation of the indanone (171). Because of these isolation difficulties, an alternative procedure was sought.

A procedure⁽¹³²⁾ in which 3-(2,5-dimethoxyphenyl)propionic acid was cyclized to (171) with phosphorus pentoxide was next investigated. Although this method was reported to give a high yield of the indanone, it was found that cyclization occurred only to a small extent.

Treatment of 4,7-dimethoxy-1-indanone with nitric acid yielded a product with an elemental analysis consistent with a mono-nitrated derivative of (171). However, a poor yield of 6-amino-4,7-dimethoxy-1-indanone hydrochloride (169) was recovered following a catalytic hydrogenation of the nitrated derivative.

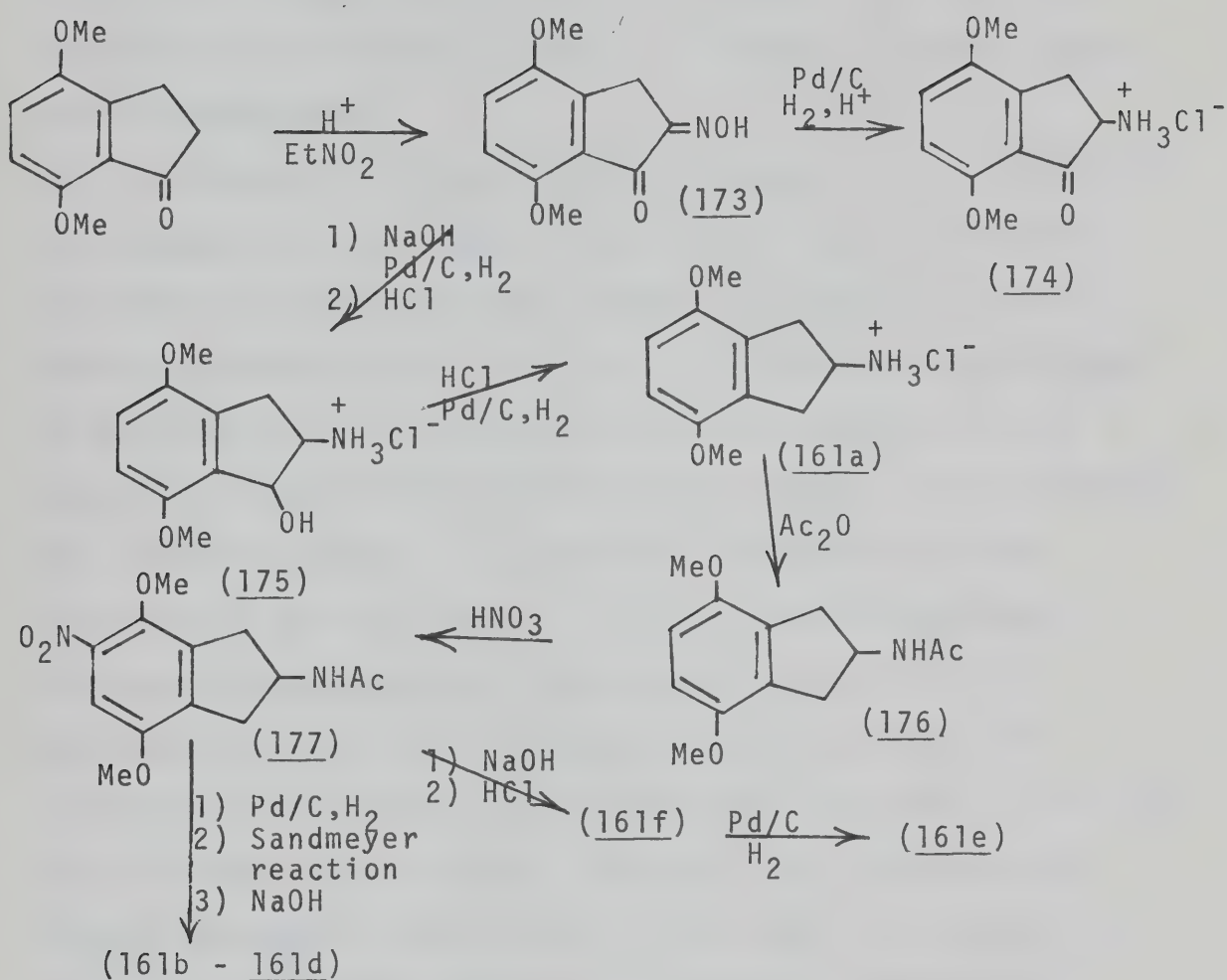


Scheme 37

An alternative method of synthesizing structures (161b - 161f) (Scheme 38) employed 2-amino-4,7-dimethoxy-indane hydrochloride (171) as starting material. 4,7-Dimethoxy-2-isonitroso-1-indanone (173) was prepared, then catalytically hydrogenated in ethanol containing hydrochloric acid and in ethanol containing sodium hydroxide to yield (174) and (175) respectively. The infrared spectrum of (175) displayed an OH absorbance band near 3350 cm^{-1} and is consistent with the expected trans-aminoalcohol (175). 2-Amino-4,7-dimethoxyindane hydrochloride (161a) was recovered after (175) was catalytically hydrogenated in hydrochloric acid. Each of the above compounds was characterized by elemental analysis and infrared spectral data.

An attempt to synthesize (161e) from 2-amino-4,7-dimethoxyindane (161a) via the intermediates (176) and (177) was unsuccessful. The acetylated derivative (176) was prepared by treating (161a) with acetic anhydride, but when 2-acetamido-4,7-dimethoxyindane was reacted with nitric acid, the only product recovered from the reaction was a red tarry material. Several unsuccessful attempts were made to isolate a pure product from the tar. Compounds (161a) and (176) were characterized by their elemental analysis as well as infrared and mass spectral data.

Since the reactions discussed so far in the attempted preparation of compounds (161b - 161f) were largely



Scheme 38

unsuccessful, further attempts to prepare them by a general scheme were discontinued and the synthesis of a specific example, namely 2-amino-5-bromo-4,7-dimethoxyindane (161c), was investigated.

2-Amino-4,7-dimethoxyindane (161a) was utilized in the preparation of (161c). By considering the directing properties of the ring substituents of (161a) to electrophilic reagents, it was felt that bromination would proceed with substitution at either of the two equivalent 5- or 6-positions to yield the desired amine (161c). This reaction was first attempted in a non-polar solvent to prevent bromination at the 5- and 6- positions from occurring. Following the addition of bromine in chloroform to a solution of 2-amino-4,7-dimethoxyindane in ethanol and chloroform, only starting material was recovered. Starting material was also recovered following the treatment of (161a) in ethanol with bromine in chloroform. However, upon adding bromine water to an ethanolic solution of the red color disappeared, indicating that a reaction was occurring. After adding a slight excess of reagent, the reaction mixture was stirred for several hours, basified, and then evaporated, leaving a dark red-black oil. A basic extraction of the oil yielded a wide melting solid which was purified with difficulty.

Alternatively a solution of 2-amino-4,7-dimethoxyindane hydrochloride in water was treated with bromine-water,

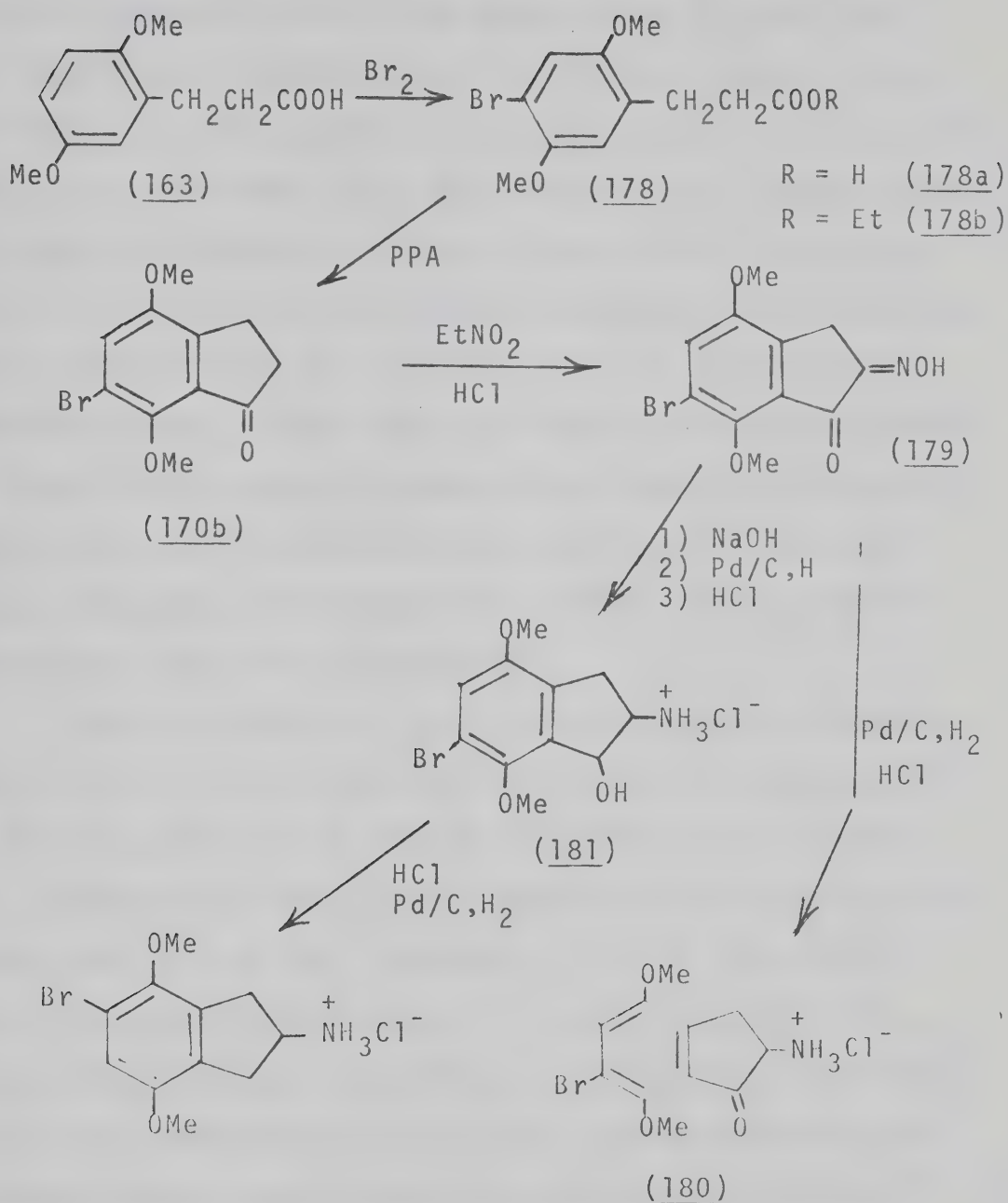
basified, then extracted with ether. The ether fraction was dried, then saturated with hydrogen chloride gas, yielding a small amount of solid material which was purified and characterized by its infrared and mass spectrum. The molecular ions in the spectrum were present at m/e 273 and at m/e 271, and both peaks were of similar intensity. This is indicative of a covalently-bonded bromine atom in the molecule. These masses correspond to the molecular weights of the ^{79}Br - and ^{81}Br -isotopes of 2-amino-5-bromo-4,7-dimethoxyindane. Although it was not proven, it was assumed that bromination had occurred at the 5-position.

Because of the low yield of product (161c) employing the bromination procedure, another route of preparing it was investigated. The route summarized by Scheme 39 appeared to be the easiest and most promising.

An attempt to synthesize 3-(4-bromo-2,5-dimethoxyphenyl)propionic acid (178a) by brominating 3-(2,5-dimethoxyphenyl)propionic acid in chloroform was unsuccessful. When bromine-water was added to a solution of 3-(2,5-dimethoxyphenyl)propionic acid in ethanol, however, bromine was incorporated. Two products were recovered; only one was soluble in 5% sodium hydroxide. The elemental analysis of the base soluble product corresponded to a mono-brominated derivative of (163). Present in the nmr spectrum of this product were two singlets in the aromatic region; this showed that bromination had occurred at the 4-position to

yield (178a). The product insoluble in 5% sodium hydroxide displayed a carbonyl absorption band characteristic of an ester in the infrared spectrum. Although this material was not further characterized, it was assumed to be the ethyl ester (178b). After hydrolysis of this material with sodium hydroxide, the carboxylic acid (178a) was isolated. Since hydrogen bromide was produced in the reaction, it obviously acted as a catalyst for esterification. To avoid formation of the ester in subsequent reactions bromination was carried out successfully employing a dioxane-water solvent system.

6-Bromo-4,7-dimethoxy-1-indanone (170b) was then prepared by cyclizing 3-(4-bromo-2,5-dimethoxyphenyl)propionic acid in polyphosphoric acid. The yield of the indanone recovered from the reaction was low. After a solution of the indanone (170b) in ethanol was saturated with hydrogen chloride gas, it was treated with ethyl nitrite. The 2-isonitroso-1-indanone which formed was then catalytically hydrogenated in an acid or basic ethanol solvent. The material isolated from the acidic solvent displayed bands in the infrared spectrum characteristic of a primary amine salt in addition to having a strong carbonyl absorption near 1710 cm^{-1} . These spectral data are in agreement with the expected structure 2-amino-6-bromo-4,7-dimethoxy-1-indanone hydrochloride (180). The material recovered following the hydrogenation of (179) in the basic solvent was dissolved in ether and saturated with gaseous



Scheme 39

hydrogen chloride. The infrared spectrum of the solid material which remained after evaporation of the ether displayed bands characteristic of a primary amine salt in addition to an OH absorption near 3350 cm^{-1} . These spectral data are in agreement with the product being trans-2-amino-6-bromo-4,7-dimethoxy-1-indanol hydrochloride (181) (see page 136). However, the elemental analyses calculated for these materials did not correspond to the experimentally obtained values. These materials were identified by means of mixed melting point determinations and infrared spectral comparisons as the corresponding debrominated compounds (174) and (175). Therefore the bromine atom was replaced by hydrogen through hydrogenolysis.

When a solution of 3-(4-bromo-2,5-dimethoxyphenyl)-propionic acid in ethanol was catalytically hydrogenated, an oil, insoluble in 5% sodium hydroxide, was recovered. The infrared spectrum of this compound displayed a carbonyl absorption at 1740 cm^{-1} indicating that it was an ester. Following hydrolysis of the oil, a solid identified as 3-(2,5-dimethoxyphenyl)propionic acid (163) was recovered. During the debromination reactions, hydrogen bromide was produced and obviously acted as a catalyst for esterification. Because of the relative ease with which debromination occurred, this synthetic route was not investigated further.

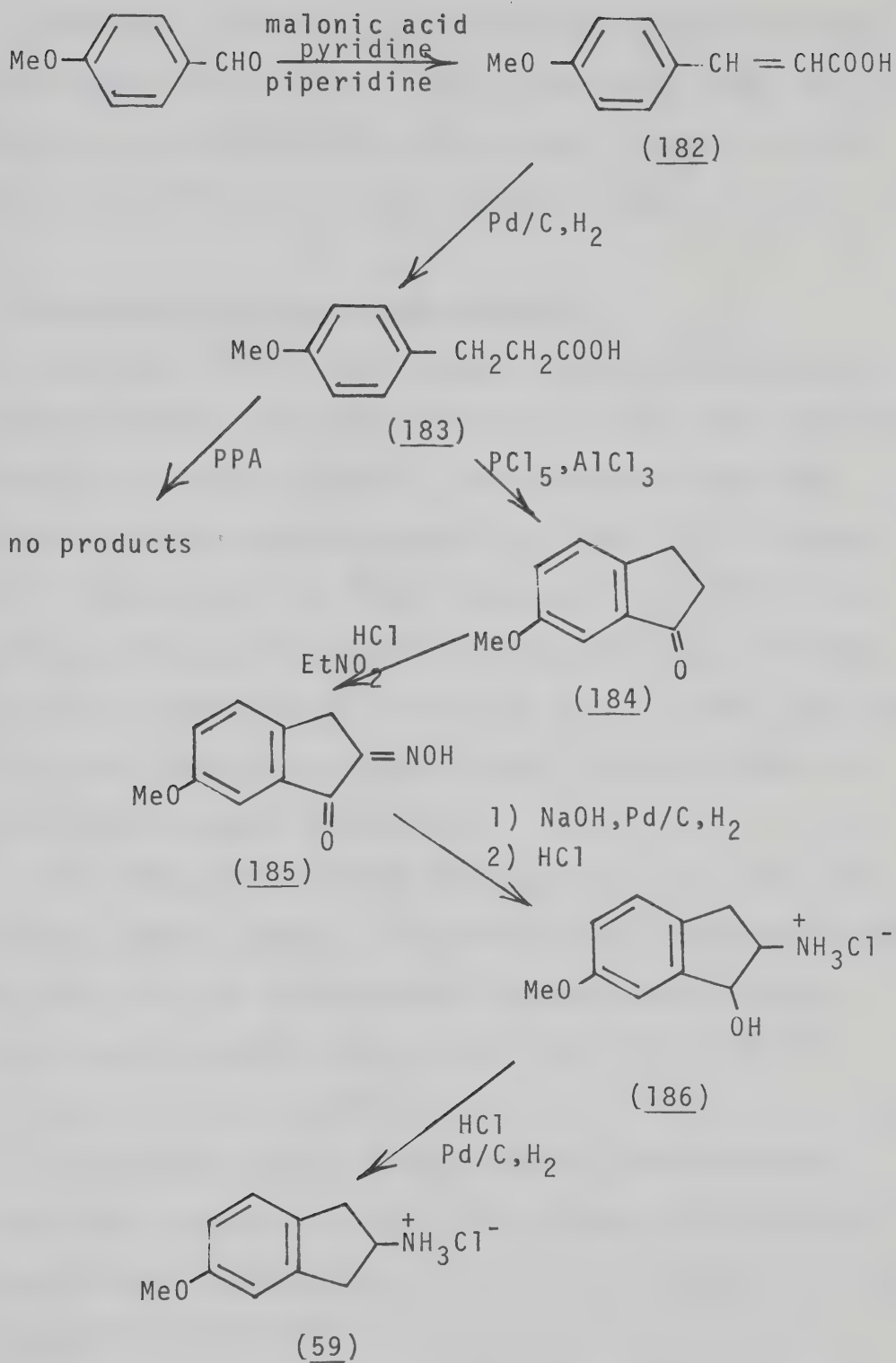
The synthesis of 2-amino-5-methoxyindane was then

studied. Since 2-(4-methoxyphenyl)isopropylamine is a known hallucinogen^(4,200), it was felt that the cyclic analog (59) might possess similar properties. This cyclic analog has been previously prepared and found to be an analgesic⁽¹¹⁸⁾, but no mention was made of its being a psychotomimetic agent.

The synthetic route used to prepare this material was similar to that described in the synthesis of 2-amino-4,7-dimethoxyindane (Scheme 40). 4-Methoxyphenylpropionic acid (183) was prepared by the method previously described, then cyclized to 6-methoxy-1-indanone (184). This cyclization reaction was attempted with polyphosphoric acid, but was unsuccessful. Treating the corresponding acid chloride with aluminum chloride yielded the indanone (184). Although this latter method is reported⁽²⁰¹⁾ to produce high yields of the indanone, only a low yield was obtained. Other workers^(122,136,202) have also reported low yields using this synthetic route.

2-Isonitroso-6-methoxy-1-indanone (185) was prepared by treating 6-methoxy-1-indanone with ethyl nitrite. Catalytic hydrogenation of this compound (185) in ethanol containing sodium hydroxide yielded 2-amino-6-methoxy-1-indanol (186).

2-Amino-5-methoxyindane hydrochloride (59) was recovered following catalytic hydrogenation of 2-amino-6-methoxy-1-indanol in hydrochloric acid.



Scheme 40

Pending a complete pharmacological study of these 2-aminoindanes, no definite conclusions about their psychopharmacological properties can be drawn. They certainly appear to be worthy of further investigation.

e) The Synthesis of Some 1-Aminoindanes

Although various substituted 1-aminoindanes (see literature survey) have been found to possess CNS activity, there are no reports in which 1-aminoindanes have been described as being psychotomimetics. Since the nitrogen atom of 1-aminoindane is fixed in a position similar to the amino group of the intramolecularly bonded structures described by Snyder et al. (see page 20), it was felt that some selected examples of substituted 1-aminoindanes may possess hallucinogenic properties.

The compounds selected for synthesis are shown by structures (188a - 188d). A pharmacological evaluation and comparison with the corresponding 2-aminoindanes could provide some meaningful data on the importance of the position of the amino group.

The method used to prepare these 1-aminoindanes involved the formation of the oxime (187a - 187d) of the corresponding 1-indanone, which was in turn reduced to the desired amine (Scheme 41).

A successful synthesis of 1-amino-4,7-dimethoxy-6-methylindane (188a) was achieved by preparing and then

reducing the oxime of 4,7-dimethoxy-6-methyl-1-indane (187a) with hydrogen in the presence of platinum dioxide or with lithium aluminum hydride. Both procedures resulted in the recovery of good yields of 1-amino-4,7-dimethoxy-6-methyl-indane.

1-Amino-4,7-dimethoxyindane (188b) was similarly prepared by treating 4,7-dimethoxy-1-indanone with hydroxylamine hydrochloride to yield the oxime (187b), which was then reduced to the indane (188b). This reduction was not as easily accomplished as in the previous example (188a). When a suspension of the oxime (187b) in ether was treated with lithium aluminum hydride, only a low yield of the amine was recovered. After a solution of the oxime in acetic acid and ethanol was catalytically hydrogenated, the desired amine was again formed in low yield. When a solution of the same oxime in a solvent of acetic acid, ethanol, and a small amount of sulfuric acid was hydrogenated in the presence of palladium-charcoal, an excellent yield of 1-amino-4,7-dimethoxyindane (188b) was recovered.

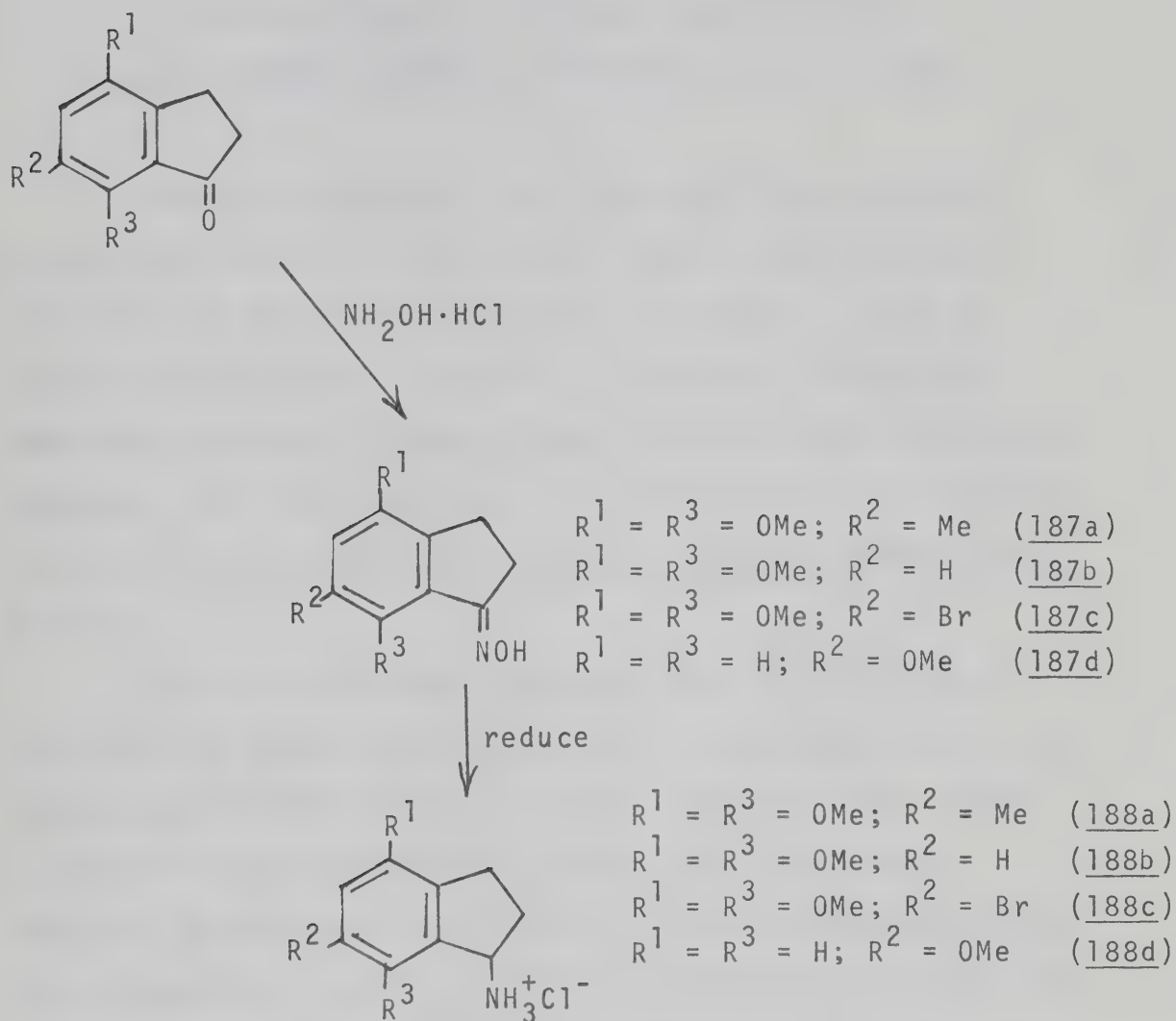
The synthesis of 1-amino-6-bromo-4,7-dimethoxyindane hydrochloride was next investigated. Since the 6-position of 2-amino-4,7-dimethoxyindane hydrochloride is the most activated ring position, this compound would be expected to incorporate bromine at this position and yield (188c).

The bromination of an aqueous solution of compound (188b) with bromine water gave the desired product in low

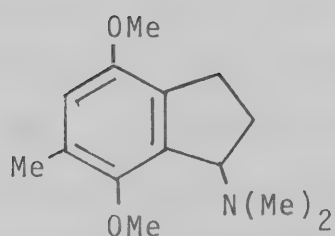
yield. After a slight excess of bromine water was added to the solution, it was stirred for several hours, basified, and then extracted with ether. The ether extract was saturated with gaseous hydrogen chloride, then evaporated, leaving an oil from which a small amount of a solid material was isolated. The molecular ion in the mass spectrum of a solid material was isolated. The molecular ion in the mass spectrum of this material was located at m/e 271, and an $(M+2)$ peak was located at m/e 273. The relative abundance of the former was approximately the same as that of the latter; this is consistent with a monobrominated derivative of (188b). Because of the small amount of product recovered the nmr spectrum was not recorded, and it was only assumed that bromination had occurred at the 6-position.

The synthesis of 1-amino-6-methoxyindane (188d) was also attempted by the method outlined in Scheme 41. The oxime (188d) was first obtained from the reaction of hydroxylamine and 6-methoxy-1-indanone, then reduced. The reduction was first attempted by catalytically hydrogenating a solution of the oxime (188d) in ethanol; no hydrogen was absorbed. When a small amount of hydrochloric acid was added to the solvent, hydrogen was rapidly incorporated. The product recovered from the reaction, although it melted near the reported one (²⁰³), analyzed indifferently for 1-amino-6-methoxyindane hydrochloride. Since this compound could not be purified, it was not characterized further.

Another derivative of 1-aminoindane, 4,7-dimethoxy-1-dimethylamino-6-methylindane (189), was also prepared. This material was recovered after 1-amino-4,7-dimethoxy-6-methylindane was treated with formaldehyde and hydrogen in the presence of palladium-charcoal as described on page 150. The infrared spectrum and elemental analysis of the product was consistent with structure (189).



Scheme 41



(189)

A PRELIMINARY PHARMACOLOGICAL SCREENING
OF SELECTED COMPOUNDS PREPARED IN THIS STUDY

During a synthetic study such as that described in this thesis, it is desirable to have some guidelines to assist in the design of active compounds. It is an unprofitable task to synthesize a series of structures chemically related to what proves to be an inactive parent compound. For this reason, some of the compounds prepared during the course of this study were examined pharmacologically.

Since the compounds prepared were designed to be psychoactive drugs, more specifically psychotomimetics, an appropriate method of detecting this activity was sought. A search of the literature revealed that the methods employed to evaluate hallucinogenic drugs were complex and time consuming. It was not the intention of this study to become deeply involved in the pharmacological evaluation of hallucinogens; therefore it was decided that only a gross pharmacological comparative study would be undertaken. This simply involved administration of the test drug to rats and comparing its gross effects relative to the known hallucinogen, DOM. It should be emphasized that the inadequacies of this testing procedure were appreciated and that the results served only to provide guidelines for the synthesis of other compounds.

Experiments are presently in progress whereby all the compounds synthesized will be tested and evaluated relative to known hallucinogens.

The effects of the test drugs were compared with those of an oral dose of DOM (10 mg/kg) in male rats (150-500 g). This dose of DOM reliably caused hypersalivation, pupillary dilation, retraction of scrotum, loss of orientating reflexes, analgesia, hypomotility, and walking with a slinking gait.

The following table summarizes the effects observed with the drugs tested. These effects were rated 0-4, where 0 means no effect observed while 4 indicates a maximal effect. A blank indicates that the effect was not examined. The degree of analgesia was determined simply by a rat's response to tail pinching.

Table IV

Comparison of the Effects of DOM (10 mg/kg)
and Some Selected Compounds Prepared in the Study

Compound (No.)	Dose mg/kg	Hypersaliv- ation	Pupil Dilation	Scrotum Retraction	Loss of Orientation Reflexes	Analgesia	Stinking Gait	Hypo- motility
1-(2,5-Dimethoxy-4-methylphenyl)isopropylamine hydrochloride (DOM) (10c)	10 (po)	4	4	4	4	4	4	4
1-(4-Bromo-2,5-dimethoxyphenyl)-isopropylamine hydrochloride (10e)	10 (po)	4	4	4	4	4	4	4
1-(4-Chloro-2,5-dimethoxyphenyl)-isopropylamine hydrochloride (10g)	10 (po)	4	4	4	4	4	4	4
1-(4-Amino-2,5-dimethoxyphenyl)-isopropylamine hydrochloride (10j)	10 (po)	0	1-2	-	0	-	0	-
1-(2,5-Dimethoxy-4-nitrophenyl)isopropylamine hydrochloride (10i)	10 (po)	4	4	4	4	4	4	4

Table IV (continued)

Compound (No.)	Dose mg/kg	Hypersaliv- ation	Pupil Dilation	Scrotum Retraction	Loss of Orientation Reflexes	Analgesia	Slinking Gait	Hypo- motility
1-(4-Acetamido-2,5-dimethoxyphenyl)-isopropylamine hydrochloride (10k)	20 (po)	0	1-2	0	0	-	0	0
N-(2,5-Dimethoxy-4-methylphenethyl)-hydroxylamine hydrochloride (87b)	60 (ip)	4	4	-	4	-	4 walked backwards	3
2,5-Dimethoxy-4-methylphenylalanine hydrochloride (100b)	40 (po)	0	0	0	0	-	0	0
Lactone of 2,5-dihydroxy-4-methylphenylalanine hydrochloride (107)	40 (ip)	0	0	0	0	-	0	hyper- active
2,5-Dimethoxy-4-methylphenylacetone (108b)	10 (po)	0	0	0	0	-	0	0
Oxime of 2,5-dimethoxy-4-methylphenylacetone hydrochloride (42)	10 (po)	0	0	0	0	-	0	0

Table IV (continued)

Compound (No.)	Dose mg/kg	Hypersaliv- ation	Pupil Dilation	Scrotum Retraction	Loss of Orientation Reflexes	Analgesia	Slinking Gait	Hypo- motility
2-Amino-4,7-dimethoxy- 5-methylindane hydrochloride (<u>141</u>)	10 (po)	4	4	4	2	-	3	3
2-Amino-5-bromo-4,7- dimethoxyindane hydrochloride (<u>161c</u>)	30 (ip)	2	2	2	2	-	3	3
2-Amino-4,7- dimethoxyindane hydrochloride (<u>161a</u>)	20 (ip)	0	1-2	0	0	-	0	1-2
2-Dimethylamino-4,7- dimethoxy-5- methylindane hydrochloride (<u>156a</u>)	10 (ip)	0	2	-	3	-	3	3
cis-2-Amino-4,7- dimethoxy-6- methyl-1-indanol hydrochloride (<u>152</u>)	30 (ip)	0	2	0	0	-	0	0
trans-2-Amino-4,7- dimethoxy-6- methyl-1-indanol hydrochloride (<u>147</u>)	30 (ip)	0	2	0	0	-	0	0

Table IV (continued)

Compound (No.)	Dose mg/kg	Hypersaliv- ation	Pupil Dilation	Scrotum Retraction	Loss of Orientation Reflexes	Analgesia	Slinking Gait	Hypo- motility
2-Amino-4,7- dimethoxy-1- ethoxyindane hydrochloride (154b)	30 (po)	0	1-2	0	2	-	0	2
1-Amino-4,7- dimethoxy-6- methylindane hydrobromide (188a)	20 (po)	0	2	0	2	-	0	2
1-Dimethylamino- methyl-4,7-dimethoxy- 6-methylindane hydrochloride (160)	20 (po)	0	2	0	2	-	0	2
2-Dimethylamino- methyl-4,7-dimethoxy- 5-methylindane hydrochloride (160)	10 (po)	0	1-2	0	2	-	1-2	1-2

po - oral administration

ip - intraperitoneal administration

In summary, no definite statements about the psychotomimetic activity of the compounds prepared can be made until they have been subjected to a thorough pharmacological investigation. However, the preliminary results indicate that several factors influence the psychotomimetic activity of phenethylamine derivatives. These factors are summarized below.

- a) Several 2,5-dimethoxy-4-substituted phenethylamines were found to be potent hallucinogens; this substitution pattern may be important for activity.
- b) Although it is thought that increasing the electron density on the phenyl ring of phenethylamines increases psychotomimetic activity, this does not appear to be completely correct. Derivatives substituted in the 4-position with electron withdrawing groups such as a nitro group appear to be extremely active.
- c) The size of the substituent at the 4-position, rather than its electron effects, appear to determine activity.
- d) As indicated by the potency of 2,5-dimethoxy-4-methylphenethylamines, it seems that decreasing the basicity does not decrease its psychotomimetic activity. In fact, this change may yield more active compounds.
- e) The cyclic analog of DOM, i.e. the corresponding 2-aminoindane, appears to be hallucinogenic. This may indicate that the alkylamino group of the phenethylamines interacts with a receptor equivalent to the N-6 nitrogen

atom of LSD.

f) The position that the nitrogen atoms of phenethylamines adopt at the receptor may correspond closely to that of the fixed nitrogen atom of 2-aminoindane. Two compounds with fixed nitrogen atoms located at similar yet different positions appear to be inactive.

g) Extending the side chain of phenethylamines beyond three carbons decreases psychotomimetic activity; substituting the analogous 1-position of 2-aminoindanes also seems to be detrimental to activity. This would suggest that the side chain of phenethylamine psychotomimetic lies in the same plane as the benzene ring when interacting with the receptor.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus. All melting points are uncorrected. Infrared (i.r.) spectra were recorded on a Beckman IR-10 spectrophotometer as Nujol mulls unless otherwise specified. Nuclear magnetic resonance (n.m.r.) spectra were taken on a Varian A-60 Spectrometer. Tetramethylsilane was used as an internal standard. Mass spectra were recorded at the Department of Chemistry, University of Alberta with an A.E.I. MS-9 or MS-12 mass spectrometer at an ionizing potential of 70 eV using the direct probe technique. Elemental analyses were determined at the Department of Chemistry and Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta.

The following abbreviations will be used throughout this section:

br = broad

d = doublet

m = multiplet

s = singlet

t = triplet

The infrared spectra of primary amine salts usually display a series of weak absorption bands between 2380 and 2770 cm^{-1} as well as a broad band near 2000 cm^{-1} (204). The exact locations of these weak bands are not given in the experimental data of each amine.

I. THE PREPARATION OF PHENETHYLAMINES
AND RELATED COMPOUNDS

a) Reactions Related to the Synthesis of 1-(2,5-Dimethoxy-4-Substituted phenyl)isopropylamines

1-Chloro-2,5-dimethoxybenzene

A solution of 1-chloro-2,5-dihydroxybenzene (11.4 g) in alcohol (60 ml) was slowly added to a solution of sodium hydroxide (8 g in 20 ml water) and dimethylsulfate (24 g). After the addition was complete (20 minutes), an additional 2 g of sodium hydroxide in water (20 ml) was added and the solution was heated under reflux for 3 hours. The mixture which remained following evaporation of the alcohol solvent was steam distilled. A clear yellow oil (9.84 g) which was assumed to be the title compound was isolated. This material has previously been reported in the literature⁽²⁰⁵⁾.

I.r. spectrum: 1030, 1215 cm^{-1} (C-O)

Anal. Calc. for $\text{C}_8\text{H}_9\text{Cl}$: C, 68.35; H, 6.45

Found: C, 68.30; H, 6.40

Attempted preparation of 4-chloro-2,5-dimethoxybenzaldehyde by formylation of 1-chloro-2,5-dimethoxybenzene

Crude 1-chloro-2,5-dimethoxybenzene (9.2 g) was added to a mixture of N-methylformanilide (17.3 g) and phosphorus oxychloride (19.6 g) which had been stirred together for 0.5 hours, and the reaction mixture was heated on a steam bath for 2 hours with occasional shaking. The reaction was carried out in a fume hood because large

volumes of hydrogen chloride gas evolved. The dark red-black viscous product was added to ice water (800 ml) and allowed to stand overnight. An oil settled to the bottom of the container, and was efficiently extracted with chloroform. The residue, after removal of the solvent, gave an orange precipitate when treated with 2,4-dinitrophenylhydrazine reagent* (2,4-DNP). Steam distillation yielded starting material (7.8 g).

The formylation reaction was repeated, except the mixture was heated under reflux employing a heating mantle. After one hour the mixture had changed to a black solid. All attempts to isolate either starting material or products failed.

1-Bromo-2,5-dimethoxybenzene

The reaction was carried out exactly as described for the preparation of 1-chloro-2,5-dimethoxybenzene. Quantities of reagents were the same except 1-bromo-2,5-dihydroxybenzene (14.5 g) was used. Steam distillation of the reaction product yielded the title compound as a clear oil (11.9 g). This compound has been previously reported in the literature⁽²⁰⁶⁾.

I.r. spectrum: $1030, 1215 \text{ cm}^{-1}$ (C-O)

* A positive test to 2,4-DNP reagent indicates the presence of an aldehyde or ketone or compounds easily oxidized to aldehydes or ketones.

Anal. Calc. for C_8H_9Br : C, 51.92; H, 4.90

Found: C, 51.95; H, 4.90

Attempted preparation of 4-bromo-2,5-dimethoxybenzaldehyde by formylation of 1-bromo-2,5-dimethoxybenzene

1-Bromo-2,5-dimethoxybenzene (10.0 g) was treated exactly the same and with the same quantities of reagents as previously described in the attempted preparation of 1-chloro-2,5-dimethoxybenzaldehyde. Steam distillation of the reaction mixture yielded 6.5 g of starting material; the residue remaining was weakly positive to 2,4-DNP reagent. Further investigation was discontinued.

Attempted preparation of 4-chloro-2,5-dihydroxybenzaldehyde by formylation of 1-chloro-2,5-dihydroxybenzene employing the Reimer-Tiemann reaction

1-Chloro-2,5-dihydroxybenzene (5.6 g) was dissolved in a solution of sodium hydroxide (10.0 g) in water (40 ml) and heated. Chloroform (20.0 g) was added to the mixture, then heated under reflux for three hours. The dark mixture was cooled and acidified with hydrochloric acid. A chloroform extract of the mixture yielded a black tarry material which was only weakly positive to 2,4-DNP reagent. This reaction was not investigated further.

2,5-Dimethoxyacetanilide

2,5-Dimethoxyaniline (5.0 g) was added to 5% hydrochloric acid (100 ml) followed by small portions of sodium

hydroxide (5%) until a slight turbidity existed. A small amount of 5% hydrochloric acid was then added to clear the solution. Acetic anhydride (50 ml) was added, and the reaction mixture was vigorously shaken until the evolution of heat ceased. Sodium acetate (25.0 g) in water (25 ml) was added in one portion, and the reaction mixture was cooled (5°) overnight. The resulting suspension was filtered, leaving the title compound (2.4 g). Extraction of the filtrate with chloroform yielded an additional 1.6 g of solid. The combined solids were crystallized from ethanol and water, m.p. 90-91°C. Reported m.p. 91°C⁽²⁰⁷⁾.

I.r. spectrum: 3250 (NH); 1660 cm^{-1} (C=O)

Anal. Calc. for $\text{C}_{10}\text{H}_{13}\text{NO}_3$: C, 61.52; H, 6.71; N, 7.18

Found: C, 61.32; H, 6.71; N, 7.18

Attempted preparation of 4-acetamido-2,5-dimethoxybenzaldehyde by formylation of 2,5-dimethoxyacetanilide

2,5-Dimethoxyacetanilide (20.0 g) was added to a previously stirred (0.5 hr) mixture of phosphorus oxychloride (40.0 g) and N-methylformanilide (35.0 g). The reaction was very exothermic with the evolution of large amounts of hydrogen chloride. The mixture was stirred at room temperature for two hours, then added to ice water. A small amount of precipitate formed and was collected by filtration. The filtrate was basified and a heavy precipitate formed. Mixed melting point determinations and i.r. spectral comparisons showed that the latter material was 2,5-dimethoxyaniline.

2,5-Dimethoxybenzyl alcohol

A solution of 2,5-dimethoxybenzaldehyde (10.0 g) in methanol (50 ml) was slowly added to a stirred solution of sodium borohydride in water (50 ml) and methanol (50 ml), then stirred for two hours. Concentrated hydrochloric acid was added to the reaction mixture until effervescence ceased. The mixture was then basified with sodium bicarbonate. The residue which remained following evaporation of the solvent was suspended in water and extracted with chloroform. Evaporation of this latter solvent left a colorless oil which was not further purified but assumed to be the title compound. This compound has been previously prepared by Harfenist and Loewe⁽²⁰⁸⁾.

I.r. spectrum: 3400 cm^{-1} br (OH); C=O stretching absorption was absent.

2,5-Dimethoxy-4-nitrobenzyl alcohol

To a solution of crude 2,5-dimethoxybenzyl alcohol (8.5 g) and sodium nitrite (0.35 g) in glacial acetic acid (100 ml) was added 70% nitric acid (12.6 ml) in water (100 ml). The solution was stirred for one hour, then diluted with ice water (300 ml). The resulting yellow suspension was filtered and the bright yellow solid (8.1 g) was crystallized from alcohol, m.p. $120-121^{\circ}\text{C}$, to yield the title compound.

I.r. spectrum: $1340, 1500\text{ (NO}_2\text{)}$; 3520 cm^{-1} (OH)

Anal. Calc. for $C_9H_{11}NO_5$: C, 50.70; H, 5.20; N, 6.57

Found: C, 50.78; H, 5.28; N, 6.50

2,5-Dimethoxy-4-nitrobenzaldehyde

A solution of 2,5-dimethoxy-4-nitrobenzyl alcohol (5.5 g) in dimethylsulfoxide (25 ml) was heated under reflux while a steady stream of air was passed through the solution for 14 hours. Additional solvent was periodically added to the reaction flask because of evaporation of the dimethylsulfoxide. Water was then added to the cooled mixture and the resulting precipitate (2.2 g) was filtered. Purification of this material from benzene yielded dark yellow crystals (1.2 g) of the title compound, m.p. 162-163°C. Reported 163-164°C⁽¹⁴⁵⁾.

I.r. spectrum: 1340, 1520 (NO_2); 1690 cm^{-1} ($C=O$)

Anal. Calc. for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63

Found: C, 50.89; H, 4.59; N, 6.10

Extraction of the filtrate with ether yielded starting material.

Attempted preparation of 4-amino-2,5-dimethoxybenzaldehyde

A solution of 2,5-dimethoxy-4-nitrobenzaldehyde (2.0 g) in ethanol (50 ml) was subjected to hydrogenation at room temperature and pressure over 10% palladium-charcoal (0.2 g). When the reaction ceased to incorporate hydrogen, the catalyst was filtered off and the ethanol was evaporated

to yield a dark brown semi-solid. Attempts to isolate the title compound were unsuccessful. The reaction was repeated; however, hydrochloric acid (1.0 ml) was added to the ethanol solvent. A similar product was isolated. Further investigations of this reaction were not undertaken.

1-(2,5-Dimethoxyphenyl)-2-nitropropene-1

A solution of 2,5-dimethoxybenzaldehyde (10.0 g) and ammonium acetate (4.0 g) in glacial acetic acid (50 ml) and nitroethane (6.8 g) was heated on a water bath for three hours, then the solvent was evaporated. The residue which remained was suspended in water and extracted with chloroform. Evaporation of the chloroform left the title compound (11.2 g). It was then crystallized from ethanol, m.p. 73-75°C. The preparation of this compound has been reported but no melting point was given⁽²⁰⁹⁾.

I.r. spectrum: 1300, 1500 (NO_2); 1645 cm^{-1} ($\text{C}=\text{C}$)

N.m.r. spectrum (DMSO-d_6): 2.33 (3 s, CH_3); 6.96 (1 m); 7.03 (2 m), aromatic protons; 8.1 δ (1 s, CH)

Anal. Calc. for $\text{C}_{11}\text{H}_{13}\text{NO}_4$: C, 59.18; H, 5.87; N, 6.28

Found: C, 58.99; H, 5.88; N, 5.95

1-(2,5-Dimethoxyphenyl)isopropylamine hydrochloride

1-(2,5-Dimethoxyphenyl)-2-nitropropene-1 (17.0 g) dissolved in sodium dried ether (500 ml) was added slowly to a stirred suspension of lithium aluminum hydride (12.0 g) in

the same solvent (150 ml). When the addition was complete, the mixture was refluxed for 20 hours, cooled, and the excess lithium aluminum hydride was decomposed by the careful addition of water. The resulting suspension was filtered and the sludge was washed with ether. The combined ether fractions were dried with magnesium sulfate, then saturated with hydrogen chloride gas. The resulting precipitate was filtered, leaving the title compound (16.3 g). This material was crystallized from ethanol, m.p. 114-117°C. Reported m.p. 111.5-112.4°C⁽¹⁷⁾.

I.r. spectrum: 1600, 2000-2550 cm^{-1} ($\text{N}^+\text{-H}$)

N-Acetyl-1-(2,5-dimethoxyphenyl)isopropylamine

Acetic anhydride (40 ml) was added to a solution of 1-(2,5-dimethoxyphenyl)isopropylamine hydrochloride (5.0 g) in water (150 ml). The mixture was shaken vigorously until the exothermic reaction ceased. Sodium acetate (25.0 g) in water (150 ml) was added to the reaction mixture which was then cooled. The resulting suspension was filtered, leaving the title compound (4.2 g). A constant melting point of 104-105.5°C was obtained by crystallization from ethanol.

I.r. spectrum: 1635 (C=O); 3310 cm^{-1} (NH)

Anal. Calc. for $\text{C}_{13}\text{H}_{19}\text{NO}_3$: C, 65.80; H, 8.07; N, 5.90

Found: C, 65.75; H, 8.13; N, 5.90

N-Acetyl-1-(2,5-dimethoxy-4-nitrophenyl)isopropylamine

A solution of 70% nitric acid (50 ml) in water (400 ml) was added to a solution of N-acetyl-1-(2,5-dimethoxyphenyl)isopropylamine (40.0 g) and sodium nitrite (0.5 g) in glacial acetic acid (400 ml). The solution was stirred four hours, cooled, then diluted with water (400 ml). The resulting suspension was filtered, leaving the title compound (42.0 g). A constant melting point of 166-168°C was obtained by crystallization from ethanol.

I.r. spectrum: 1350, 1515 (NO_2); 1640 (C=O);
3310 cm^{-1} (NH)

N.m.r. spectrum (CDCl_3): 1.16 (3 d, $J = 7$ cps, $\alpha\text{-CH}_3$); 1.88 (3 s, acetyl protons); 2.85 (2 d, $J = 7$ cps, CH_2); 3.85 (3 s), 3.90 (3 s), OCH_3 protons; 4.5-4.0 (1 m, CH); 5.91-5.66 (1 m, NH); 6.97 (1 s), 7.41 δ (1 s), aromatic protons

Anal. Calc. for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_5$: C, 55.31; H, 6.43;
N, 9.92

Found: C, 55.26; H, 6.63;
N, 9.92

N-Acetyl-1-(4-amino-2,5-dimethoxyphenyl)isopropylamine hydrochloride

A solution of N-acetyl-1-(2,5-dimethoxy-4-nitrophenyl)isopropylamine (39.0 g) was hydrogenated over 10% palladium-charcoal (1.0 g) for three days. The theoretical amount of hydrogen was absorbed. The catalyst was filtered

off and the solvent removed. A solution of 5% sodium hydroxide (100 ml) was added and the suspension was then extracted with chloroform. The chloroform extract was evaporated and the solid residue was dissolved in ether. Addition of gaseous hydrogen chloride to this solution caused the precipitation of the title compound (31.5 g). Crystallization of this material from ethanol and ether resulted in a constant melting point 237-239°C.

I.r. spectrum: 1635 (C=O); 2450-2600 ($\text{N}^+\text{-H}$);
3310 cm^{-1} (NH)

Anal. Calc. for $\text{C}_{13}\text{H}_{21}\text{ClN}_2\text{O}_3$: C, 54.07; H, 7.33;
N, 9.70

Found: C, 54.18; H, 7.40;
N, 9.78

N-Acetyl-1-(4-chloro-2,5-dimethoxyphenyl)isopropylamine

A solution of N-acetyl-1-(4-amino-2,5-dimethoxyphenyl)isopropylamine hydrochloride (5.0 g) in hydrochloric acid (30 ml) and water (30 ml) was cooled to 0° in an ice bath. To this stirred solution was slowly added sodium nitrite (1.4 g) in water (10 ml). This cold solution of diazonium compound was added slowly, with shaking, to a previously prepared cuprous chloride solution (2.5 g cuprous chloride in 9 ml hydrochloric acid). The reaction mixture was allowed to come to room temperature, heated on a water bath to 70°, then cooled. The precipitate which formed was

the title compound (2.8 g). It was recrystallized from ethanol and had a m.p. of 150-152 °C.

I.r. spectrum: 1630 (C=O); 3310 cm^{-1} (NH)

N.m.r. spectrum (CDCl_3): 1.11 (3 d, J = cps, $\alpha\text{-CH}_3$); 1.85 (3 s, acetyl protons); 4.6 (2 d, J = 7 cps, CH_2); 3.79 (3 s), 3.80 (3 s) OCH_3 protons; 4.2 (1 m, CH); 5.96 (1 br s, NH) 6.76 (1 s), 6.9 δ (1 s), aromatic protons

Anal. Calc. for $\text{C}_{13}\text{H}_{18}\text{ClNO}_3$: C, 57.46; H, 6.68;

N, 5.16

Found: C, 57.35; H, 6.48;

N, 5.33

N-Acetyl-1-(2,5-dimethoxy-4-iodophenyl)isopropylamine

To a solution of N-acetyl-1-(4-amino-2,5-dimethoxyphenyl)isopropylamine hydrochloride (5.0 g) in hydrochloric acid (15 ml), cooled to 0° in an ice bath, was slowly added a solution of sodium nitrite (4.0 g) in water (8 ml). A solution of potassium iodide (8.0 g) in water (10 ml) was gradually added to the solution of the diazonium chloride. The reaction mixture was allowed to warm to room temperature until the evolution of nitrogen ceased. The aqueous portion of the reaction mixture was decanted from the dark brown viscous semi-solid which separated out of solution. This material was dissolved in ethanol and cooled. A crystalline material formed and was filtered (1.97 g). Attempts to isolate more solid material failed. Crystallization of the

solid material from ethanol yielded the title compound,
m.p. 167-168°C.

I.r. spectrum: 1645 (C=O); 3310 cm^{-1} (NH)

Anal. Calc. for $\text{C}_{13}\text{H}_{18}\text{INO}_3$: C, 42.99; H, 4.99;

N, 3.86

Found: C, 43.00; H, 5.00;

N, 3.77

N-Acetyl-1-(4-bromo-2,5-dimethoxyphenyl)isopropylamine

A slight excess of bromine-water was added to
N-acetyl-1-(2,5-dimethoxyphenyl)isopropylamine (3.0 g) in
ethanol or dioxane (30 ml). The reaction was stirred
several hours, then the solvent evaporated, leaving the
title compound (2.7 g). It was crystallized from ethanol
and a constant melting point of 153-155°C was obtained.

I.r. spectrum: 1630 (C=O); 3310 cm^{-1} (NH)

N.m.r. spectrum (CDCl_3): 1.16 (3 d, $J = 7$ cps,
 $\alpha\text{-CH}_3$); 1.90 (3 s, acetyl protons); 4.41 (2 d, $J = 7$ cps,
 CH_2); 3.81 (3 s), 3.85 (3 s), OCH_3 protons; 3.9-4.5 (1 m, CH);
5.91 (1 br s, NH); 6.80 (1 s), 7.07 δ (1 s), aromatic
protons

Mass spectrum: 317(5) [$\text{C}_{13}\text{H}_{18}^{81}\text{BrNO}_3$]; 315(5)
[$\text{C}_{13}\text{H}_{18}^{79}\text{BrNO}_3$]; m/e (% rel. abund.)

Anal. Calc. for $\text{C}_{13}\text{H}_{18}\text{BrNO}_3$: C, 49.38; H, 5.74

Found: C, 49.38; H, 5.85

Attempted hydrolysis of N-acetyl-1-(4-amino-2,5-dimethoxyphenyl)isopropylamine with hydrochloric acid

A solution of N-acetyl-1-(4-amino-2,5-dimethoxyphenyl)isopropylamine (5.0 g) in ethanol (100 ml) and hydrochloric acid (100 ml) was heated under reflux four hours. Removal of the solvent yielded starting material (mixed melting showed no depression). The same amide (50 g) was heated under reflux for 15 hours in a solution of hydrochloric acid (100 ml) and water (100 ml). The solvent was removed, and fractional crystallization yielded 0.6 g of a crystalline material, m.p. 248-255°C. Crystallization from a variety of solvent systems (ethanol, ethanol-ether, and ethanol-acetone) failed to provide a sharp melting compound.

I.r. spectrum: (C=O) was absent.

Hydrolysis of N-acetyl-1-(2,5-dimethoxy-4-nitrophenyl)-isopropylamine with hydrochloric acid

A suspension of N-acetyl-1-(2,5-dimethoxy-4-nitrophenyl)isopropylamine (5.0 g) was heated at reflux temperature in hydrochloric acid (60 ml) and water (60 ml) for two hours; after this period of time solution had not occurred. Refluxing the mixture for 15 hours resulted in a considerable amount of the original suspension going into solution. The suspension was filtered and the solvent was evaporated, leaving a yellow solid (1.7 g). The solid was washed with acetone, then crystallized from ethanol-ether yielding

1-(2,5-dimethoxy-4-nitrophenyl)isopropylamine hydrochloride,
m.p. 203-204°C.

I.r. spectrum: 1340, 1520 (NO_2); 1610, 2000, 2500-
2690 (N-H^+)

Anal. Calc. for $\text{C}_{11}\text{H}_{17}\text{ClN}_2\text{O}_4$: C, 47.74; H, 6.19;
N, 10.13

Found: C, 47.98; H, 6.33;
N, 10.01

Hydrolysis of N-acetyl-1-(4-bromo-2,5-dimethoxyphenyl)-
isopropylamine with hydrochloric acid

Treatment of N-acetyl-1-(4-bromo-2,5-dimethoxyphenyl)-
isopropylamine (2.5 g) in hydrochloric acid (60 ml) exactly
as described in the above reaction yielded 1-(4-bromo-2,5-
dimethoxyphenyl)isopropylamine hydrochloride (1.7 g). The
material was recrystallized from ethanol-ether, m.p. 195-
196°C. Reported m.p. 198-199°C⁽¹⁶⁾.

I.r. spectrum: 1610, 1980, 2010-2740 cm^{-1} (N-H^+)

Anal. Calc. for $\text{C}_{11}\text{H}_{17}\text{BrClNO}_2$: C, 42.53; H, 5.52;
N, 4.51

Found: C, 42.86; H, 5.72;
N, 4.29

Attempted hydrolysis of N-acetyl-1-(4-bromo-2,5-
dimethoxyphenyl)isopropylamine with sulfuric acid

N-Acetyl-1-(4-bromo-2,5-dimethoxyphenyl)isopropyl-
amine (2.5 g) was stirred at room temperature with sulfuric

acid (30 ml) for two hours, then diluted with ice water (100 ml) and extracted with chloroform. Evaporation of the chloroform solution left starting material (2.3 g).

Heating a solution of the same amide (2.5 g) in 50% H_2SO_4 (50 ml) caused the reaction mixture to turn a very dark color. Attempts to isolate any amine failed.

Attempted hydrolysis of N-acetyl-1-(4-bromo-2,5-dimethoxyphenyl)isopropylamine with sodium hydroxide

A suspension of N-acetyl-1-(4-bromo-2,5-dimethoxyphenyl)isopropylamine (2.5 g) in 10% sodium hydroxide (100 ml) was heated under reflux for 15 hours, cooled, and extracted with chloroform. This chloroform extract was in turn extracted with 5% hydrochloric acid. Evaporation of the acid solvent provided a negligible amount of residue. The above reaction was repeated except sufficient dioxane was added to the refluxing suspension to achieve solution. These conditions again failed to hydrolyze the compound.

Hydrolysis of N-acetyl-1-(4-bromo-2,5-dimethoxyphenyl)-isopropylamine with sodium hydroxide

A solution of N-acetyl-1-(4-bromo-2,5-dimethoxyphenyl)isopropylamine (1.0 g), sodium hydroxide (5.0 g) in water (25 ml) and ethylene glycol (50 ml) was heated under reflux for four hours, then cooled. The reaction mixture was extracted with chloroform. The solid remaining after the chloroform was evaporated was dissolved in 5% hydro-

chloric acid (50 ml), filtered, then evaporated, leaving 1-(4-bromo-2,5-dimethoxyphenyl)isopropylamine hydrochloride (0.22 g), m.p. 197-198°C.

Extending the reaction time to 20 hours afforded 0.45 g of product, and after 30 hours 0.46 g of the amine was recovered.

Attempted hydrolysis of N-acetyl-1-(4-amino-2,5-dimethoxyphenyl)isopropylamine with sodium hydroxide

A suspension of N-acetyl-1-(4-amino-2,5-dimethoxyphenyl)isopropylamine (2.5 g) was heated under reflux in 10% sodium hydroxide. The suspension was filtered and a solid formed in the filtrate (0.82 g). This solid was dissolved in ether and gaseous hydrogen chloride was passed through the solution. A precipitate formed, m.p. 240-250°C. Mixed melting point determination with the product isolated from the acid hydrolysis of the same amide failed to show any depression in melting. As previously experienced, it was also difficult to obtain a sharp melting point.

General procedure to hydrolyze N-acetyl-1-(4-substituted-2,5-dimethoxyphenyl)isopropylamines

The appropriate amide (1.0 g) and sodium hydroxide (5.0 g) in water (25 ml) and ethylene glycol (50 ml) was heated under reflux for 15 hours, then cooled. The mixture was then extracted with chloroform, washed with water, then evaporated. The solid material remaining was dissolved in

5% hydrochloric acid (15 ml), filtered, and then evaporated, leaving the amine hydrochloride.

1-(2,5-Dimethoxy-4-nitrophenyl)isopropylamine
hydrochloride

N-Acetyl-1-(2,5-dimethoxy-4-nitrophenyl)isopropylamine (2.0 g) was treated as described by the general procedure to yield the title compound (0.76 g), m.p. 202-204°C. Mixed melting point determination with the title compound isolated earlier (page 195) was undepressed.

1-(4-Amino-2,5-dimethoxyphenyl)isopropylamine
hydrochloride

N-Acetyl-1-(4-amino-2,5-dimethoxyphenyl)isopropylamine (2.0 g) was subjected to the conditions described in the general procedure to yield the title compound (0.89 g), m.p. 240-250°C. This material was difficult to crystallize to a sharp melting point. An alternative approach was therefore sought. 1-(2,5-Dimethoxy-4-nitrophenyl)isopropylamine hydrochloride (1.0 g) was dissolved in ethanol (25 ml) and hydrochloric acid (2.0 ml), then hydrogenated over 10% palladium-charcoal (0.1 g) until the theoretical amount of hydrogen was absorbed. The catalyst was removed by filtration, and the solvent was evaporated, leaving a quantitative yield of 1-(4-amino-2,5-dimethoxyphenyl)isopropylamine dihydrochloride. Recrystallization from ethanol-ether afforded the pure compound, m.p. 248-250°C.

I.r. spectrum: 1610, 2010, 2500-2610 cm^{-1} (N-H^+)

Anal. Calc. for $\text{C}_{11}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_2$: C, 46.65; H, 7.12;

N, 9.89

Found: C, 46.98; H, 7.36;

N, 9.63

1-(4-Bromo-2,5-dimethoxyphenyl)isopropylamine
hydrochloride

N-Acetyl-1-(4-bromo-2,5-dimethoxyphenyl)isopropyl-amine (1.5 g) was treated as described in the general procedure. The title compound was isolated (0.85 g) and crystallized from ethanol-ether, m.p. 195-196°C. A mixed melting point determination with the title compound isolated on page 195 was undepressed.

1-(4-Chloro-2,5-dimethoxyphenyl)isopropylamine
hydrochloride

N-Acetyl-1-(4-chloro-2,5-dimethoxyphenyl)isopropyl-amine (1.5 g) was treated according to the general procedure and yielded the title compound (0.46 g), m.p. 193-194.5°C (ethanol-ether).

I.r. spectrum: 1610, 2010, 2500-2640 cm^{-1} (N-H^+)

Anal. Calc. for $\text{C}_{11}\text{H}_{17}\text{Cl}_2\text{NO}_2$: C, 49.63; H, 6.44;

N, 5.44

Found: C, 49.79; H, 6.70;

N, 5.44

1-(2,5-Dimethoxy-4-iodophenyl)isopropylamine
hydrochloride

N-Acetyl-1-(2,5-dimethoxy-4-iodophenyl)isopropylamine (1.5 g) was hydrolyzed by the general procedure. The title compound was isolated (0.75 g), then crystallized from ethanol and ether to a constant m.p. of 198-200°C.

I.r. spectrum: 1605, 2000, 2500-2710 cm^{-1} (N-H)⁺

Anal. Calc. for $\text{C}_{11}\text{H}_{17}\text{ClINO}_2$: C, 36.94; H, 4.79;
N, 3.93

Found: C, 36.68; H, 4.75;
N, 3.93

Catalytic reduction of 1-(2,5-dimethoxyphenyl)-2-nitropropene-1

A solution of 1-(2,5-dimethoxyphenyl)-2-nitropropene-1 (7.0 g) in ethanol (150 ml) was hydrogenated at room temperature and pressure in the presence of palladium-charcoal (0.7 g). After approximately three hours the uptake of hydrogen ceased. The mixture was filtered and the solution evaporated, leaving a light yellow oil which was positive to 2,4-DNP reagent. A solution of the oil in chloroform (100 ml) was extracted with 5% hydrochloric acid. The oil which remained following evaporation of the chloroform was distilled under reduced pressure to yield 2,5-dimethoxyphenylacetone (2.3 g), b.p. .07 mm 100°C. This compound has previously been reported in the literature⁽²⁰⁹⁾.

I.r. spectrum: 1710 cm^{-1} (C=O)

N.m.r. spectrum (CDCl_3): 1.95 (3 s, CH_3); 3.45 (2 s, CH_2); 4.25 (6 s, OCH_3 protons); 6-6.6 δ (3 m, aromatic protons)

Anal. Calc. for $\text{C}_{11}\text{H}_{14}\text{O}_3$: C, 68.02; H, 7.26

Found: C, 67.87; H, 7.25

Another fraction of the distillate (2.4 g, b.p. .13-.15 mm, 150-170°C) was isolated. It was dissolved in ether, then saturated with gaseous hydrogen chloride. The resulting precipitate (1.2 g) was collected and crystallized from acetone and ether to yield the hydrochloride salt of the oxime of 2,5-dimethoxyphenylacetone, m.p. 94-97°C.

I.r. spectrum: 2560 cm^{-1} br ($\text{N}^+\text{-H}$)

Mass spectrum: 209 (55) [$\text{C}_{11}\text{H}_{15}\text{NO}_3$]; 178 (100) [$\text{C}_8\text{H}_{10}\text{NO}_2$]; m/e (% rel. abund.)

Anal. Calc. for $\text{C}_{11}\text{H}_{16}\text{ClNO}_3$: C, 53.55; H, 6.96;

N, 5.68

Found: C, 53.87; H, 6.75;

N, 5.98

2,5-Dimethoxy-4-nitrophenylacetone

To a solution of 2,5-dimethoxyphenylacetone (4.0 g) and sodium nitrite (0.03 g) in glacial acetic acid (25 ml), which had been stirred and cooled to 5°C, was slowly added a solution of 80% nitric acid (6 ml) in water (15 ml). The reaction mixture was stirred for two hours, then diluted with water (100 ml). This caused the formation of a heavy yellow precipitate (3.71 g). Crystallization from ethanol

afforded the title compound, m.p. 77-79°C.

I.r. spectrum: 1350, 1515 (NO_2); 1730 cm^{-1} (C=O)

N.m.r. spectrum (CDCl_3): 2.23 (3 s, CH_3); 3.8 (2 s, CH_2); 3.85 (3 s), 3.92 (3 s), OCH_3 protons; 6.98 (1 s), 7.45 δ (1 s), aromatic protons

Anal. Calc. for $\text{C}_{11}\text{H}_{14}\text{ClNO}_3$: C, 55.23; H, 5.48;
N, 5.86

Found: C, 55.00; H, 5.42;
N, 5.93

4-Amino-2,5-dimethoxyphenylacetone hydrochloride

A solution of 2,5-dimethoxy-4-nitrophenylacetone (3.5 g) in ethanol (100 ml) and hydrochloric acid (5 ml) was hydrogenated at room temperature and normal pressure under 10% palladium charcoal (1.0 g) until the theoretical amount of hydrogen was absorbed. The catalyst was removed by filtration and the solvent was evaporated *in vacuo*, leaving a white solid (3.1 g). Crystallization from ethanol-ether afforded the title compound, m.p. 195-198°C.

I.r. spectrum: 1711 cm^{-1} (C=O); 1980, 2550 cm^{-1} (N-H^+)

Anal. Calc. for $\text{C}_{11}\text{H}_{16}\text{ClNO}_3$: C, 53.77; H, 6.55;
N, 5.70

Found: C, 53.85; H, 6.40;
N, 6.03

4-Acetamido-2,5-dimethoxyphenylacetone

A solution of 4-amino-2,5-dimethoxyphenylacetone hydrochloride (3.0 g) in water (30 ml) and acetic anhydride (15 ml) was shaken vigorously until the evolution of heat ceased. Sodium acetate (10.0 g) in water (10 ml) was added to the reaction in one portion, then cooled. The resulting suspension was filtered, leaving the title compound (1.7 g). Extraction of the filtrate with chloroform (100 ml), followed by its evaporation, yielded an additional 0.7 g of the acetylated product. The combined samples were crystallized from ethanol, m.p. 138-140°C.

I.r. spectrum: 1670 (amide C=O); 1710 (ketone C=O); 3390 cm^{-1} (NH)

Anal. Calc. for $\text{C}_{13}\text{H}_{17}\text{NO}_4$: C, 62.13; H, 6.82; N, 5.58

Found: C, 61.81; H, 6.67; N, 5.92

4-Acetamido-2,5-dimethoxyphenylacetone oxime

A solution of 4-acetamido-2,5-dimethoxyphenylacetone (1.5 g) and hydroxylamine hydrochloride (2.0 g) in ethanol (20 ml) and pyridine (1.0 ml) was heated on a water bath for 20 minutes. The solvent was evaporated under reduced pressure, leaving an oil. The i.r. spectrum of the oil showed that a large portion of the ketone was present. The same solution was heated under reflux for two hours. The i.r. of the oil, after removal of the solvent, again showed that a considerable portion of the ketone was present.

When the same solution was heated under reflux for 13 hours (overnight) the reaction turned a very dark color; removal of the solvent left a black oil. The i.r. spectrum of the oil failed to display a carbonyl stretching frequency.

After repeated attempts to isolate pure products failed, the mixture was hydrogenated at room temperature and 45 psi under platinum oxide (0.1 g). It failed to incorporate hydrogen. Further investigations of this oil were not undertaken.

Another solution of 4-acetamido-2,5-dimethoxyphenyl-acetone (2.0 g) and hydroxylamine hydrochloride (2.0 g) in ethanol (30 ml) and pyridine (5 ml) was heated at 75° on a water bath for seven hours. The solvent was removed under reduced pressure. Water was then added to the residue, and subsequently extracted with chloroform. The chloroform solution was evaporated and yielded a pale yellow oil. Addition of ether to the oil caused it to solidify (1.4 g). Recrystallization from ethanol yielded the title compound, m.p. 140-144°C.

I.r. spectrum: 1660 (C=O); 3250 cm^{-1} br (OH)

Anal. Calc. for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_4$: C, 58.63; H, 6.81;
N, 10.52

Found: C, 58.63; H, 7.01;
N, 10.29

1-(4-Acetamido-2,5-dimethoxyphenyl)isopropylamine
hydrochloride

A solution of 4-acetamido-2,5-dimethoxyphenylacetone oxime (1.0 g) in ethanol (50 ml) and hydrochloric acid (1.0 ml) was hydrogenated at room temperature and 50 psi pressure in the presence of platinum dioxide (0.1 g) for 14 hours (arbitrary). The solvent was evaporated after the catalyst was removed by filtration and a solid remained. Recrystallization from ethanol and ether yielded the title compound (0.72 g), m.p. 249-250°C.

I.r. spectrum: 1600, 2500-2700 (N-H^+); 1660 (C=O); 3250 cm^{-1} (NH)

Anal. Calc. for $\text{C}_{13}\text{H}_{21}\text{ClN}_2\text{O}_3$: C, 54.07; H, 7.33;
N, 9.70

Found: C, 54.35; H, 7.85;
N, 9.64

b) Reactions Related to the Synthesis of Some Analogs
of 1-(2,5-dimethoxy-4-methylphenyl)isopropylamine (DOM)

2,5-Dimethoxytoluene

Dimethylsulfate (6.75 g) and sodium hydroxide solution (3.0 g in 10 ml water) were separately added in five aliquots over 30 minutes to a stirred solution of 2,5-dihydroxytoluene (13.0 g) in methanol (50 ml). An additional 1.5 g of sodium hydroxide was then added and the mixture was heated under reflux for three hours.

The methanol was evaporated and the remaining aqueous portion was steam distilled. The title compound (12.2 g) separated from the distillate. The i.r. spectrum of this material was superimposable on that of an authentic commercial sample of 2,5-dimethoxytoluene (City Chemical Corporation).

2,5-Dimethoxy-4-methylbenzaldehyde

2,5-Dimethoxytoluene (15.2 g) was added to a previously stirred (0.5 hr) solution of N-methylformanilide (35.0 g) and phosphorus oxychloride (40.0 g). After the reaction mixture was heated on a steam bath for three hours, it was poured into ice water (300 ml). The oil that originally formed crystallized on standing. This compound was collected by filtration, then washed with cold water and cold ethanol, leaving the title compound (14.0 g). The material was crystallized from ethanol, m.p. 83-84°C. Reported m.p. 84-85°C⁽²¹⁰⁾.

I.r. spectrum: 1660 cm^{-1} (C=O)

N.m.r. spectrum (CDCl_3): 2.25 (3 s, CH_3); 3.85 (3 s), 3.88 (3 s), OCH_3 protons; 6.75 (1 s), 7.18 δ (1 s), aromatic protons

Anal. Calc. for $\text{C}_{10}\text{H}_{12}\text{O}_3$: C, 66.59; H, 6.71

Found: C, 66.56; H, 6.72

2,5-Dimethoxy-4-methyl- β -nitrostyrene

A solution of 2,5-dimethoxy-4-methylbenzaldehyde (17.0 g) and nitromethane (6.0 g) in methanol (400 ml) in a 2 litre flask fitted with a mechanical stirrer, a thermometer and a separatory funnel, was cooled in an ice-salt bath to 50°. A cooled solution of sodium hydroxide (8.0 g in 200 ml water) was added from the separatory funnel at a rate to maintain the temperature of the reaction mixture at 10-15°. The thick precipitate that formed was diluted with methanol (100 ml), then stirred for 15 minutes. The addition of ice water (1 litre) dissolved the suspension. The mixture was then added to a solution of hydrochloric acid (200 ml) and water (300 ml) in a steady flow from a separatory funnel. The yellow crystalline material which separated was filtered, then washed with water. Crystallization of this product from ethanol yielded the title compound (21.0 g), m.p. 116°C. Reported m.p. 111-112°C⁽¹⁸⁾.

I.r. spectrum: 1350, 1500 (NO_2); 1620 cm^{-1} ($\text{C}=\text{C}$)

Anal. Calc. for $\text{C}_{11}\text{H}_{13}\text{NO}_4$: N, 6.28

Found: N, 6.12

2,5-Dimethoxy-4-methylphenethylamine hydrochloride

2,5-Dimethoxy-4-methyl- β -nitrostyrene (1.0 g) in sodium dried ether (50 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (0.5 g) in the same solvent (50 ml). The suspension was then heated under

reflux for three hours. The excess lithium aluminum hydride was decomposed by the careful addition of water. The resulting heavy suspension was filtered and the sludge washed well with ether. The combined ether fractions were dried with sodium sulfate, then saturated with gaseous hydrogen chloride. The copious precipitate was collected (0.64 g) and crystallized from ethanol and ether to yield the title compound, m.p. 210-212°C. Reported m.p. 212-213°C⁽¹⁸⁾.

I.r. spectrum: 1605, 2020, 2640-2780 cm^{-1} (N-H^+)

Reduction of 2,5-dimethoxy-4-methyl- β -nitrostyrene with sodium borohydride

A solution of 2,5-dimethoxy-4-methyl- β -nitrostyrene (15.0 g) was added to a stirred solution of sodium borohydride (5.0 g) in water (25 ml) and dioxane (25 ml) at such a rate that decolorization occurred between additions. After the addition was completed, the light yellow solution was stirred for one hour, cooled, and hydrochloric acid carefully added until effervescence ceased. The solvent was evaporated and water (100 ml) and chloroform (100 ml) were added to the residue. The chloroform solution was collected and evaporated to give a dark brown oil which was dissolved in ethanol, and allowed to stand 24 hours during which time a brown crystalline solid formed (10.5 g). Stirring the crude solid in ethanol with mild heating gave two products. An ethanol-insoluble compound was separated

by filtration. The ethanolic solution was concentrated and allowed to crystallize, yielding 1-(2,5-dimethoxy-4-methylphenyl)-2-nitroethane (7.9 g), m.p. 67-70°C.

I.r. spectrum: 1370, 1550 (NO_2)

N.m.r. spectrum (CDCl_3): 2.2 (3 s, CH_3); 4.91 (2 t, $J = 8$ cps, CH_2); 4.58 (2 t, $J = 8$ cps, CH_2); 6.63 (1 s), 6.68 δ (1 s), aromatic protons

Anal. Calc. for $\text{C}_{11}\text{H}_{15}\text{NO}_4$: C, 58.65; H, 6.71; N, 6.22

Found: C, 58.32; H, 7.06; N, 6.10

The ethanol-insoluble product (2.8 g) was crystallized from dioxane to yield 2,4-di(2,5-dimethoxy-4-methylphenyl)-1,3-dinitrobutane, m.p. 167.5-169°C.

I.r. spectrum: 1370, 1550 cm^{-1} (NO_2)

Mass spectrum: 448 (27) [$\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_8$];

m/e (% rel. abund.)

N-(2,5-Dimethoxy-4-methylphenethyl)hydroxylamine hydrochloride

A solution of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitroethane (1.5 g) in ethanol (50 ml) and water (10 ml) was stirred with ammonium chloride (1.5 g) and zinc powder (1.5 g), then heated under reflux for five minutes. The insoluble portion was removed by filtration and the clear filtrate was evaporated. A 5% sodium bicarbonate solution (50 ml) was added to the residue prior to thorough extraction with chloroform. The organic solvent was saturated with gaseous hydrogen chloride, and evaporated,

leaving a solid residue. Water was added to the residue and the suspension was filtered. Addition of ammonium hydroxide to the filtrate caused the precipitation of a white material which was then extracted with chloroform. The chloroform fraction was collected, washed well with water, then saturated with gaseous hydrogen chloride. Removal of the solvent left 0.52 g of a solid residue. Crystallization from ethanol-ether yielded the title compound, m.p. 137-138°C.

I.r. spectrum: 1610, 2510-2750 (N-H);
3050 cm^{-1} br (OH)

Mass spectrum: 211 (10) [$\text{C}_{10}\text{H}_{17}\text{NO}_3$];
m/e (% rel. abund.)

Anal. Calc. for $\text{C}_{11}\text{H}_{18}\text{ClNO}_3$: C, 53.33; H, 7.32;
N, 5.66

Found: C, 53.18; H, 7.57;
N, 5.57

Attempted synthesis of N-(2,5-dimethoxy- α ,4-dimethyl-phenethyl)hydrazine

A solution of hydrazine 95% (1.2 g) in methanol was added rapidly in one batch to a refluxing solution of 2,5-dimethoxy-4-methylphenylacetone (2.0 g) in methanol (50 ml). The solution was heated under reflux for one hour. Evaporation of the solvent left an oil whose i.r. spectrum failed to display a carbonyl absorption. In an attempt to prepare the hydrochloride salt, the oil was dissolved in

ether, then saturated with hydrogen chloride gas. Evaporation of the ether left another oil which did not crystallize. It was then dissolved in methanol (50 ml) and acetic acid (5 ml), and hydrogenated at room temperature and 50 psi in the presence of platinum dioxide (0.05 g) for three hours. The catalyst was removed and the solvent evaporated to yield an oily residue which was suspended in 5% sodium bicarbonate (25 ml) and extracted with chloroform. The chloroform layer was washed well with water, then extracted with a 5% hydrochloric acid solution (15 ml). Evaporation of the latter solvent left a solid material (0.36 g) which had an i.r. spectrum superimposable on that of 1-(2,5-dimethoxy-4-methylphenyl)isopropylamine hydrochloride. A mixture of these materials did not result in a depression of the melting point.

Evaporation of the chloroform extract left a red oil which was positive to 2,4-DNP reagent.

I.r. spectrum: 1710 cm^{-1} (C=O)

Mass spectrum: 238 (2); 236 (2); 230 (<2); 228 (<2); 210 (6); 208 (16); 194 (15); m/e (% rel. abund.)

The reaction described immediately above was repeated. A basic compound (0.7 g) was isolated from the reaction mixture. Crystallization from ethanol yielded the isopropylhydrazone of 2,5-dimethoxy-4-methylphenylacetone hydrochloride.

I.r. spectrum: 1660 (N=N); 2450 br,
2610 cm^{-1} br (N-H^+)

N.m.r. spectrum (DMSO-d_6): 1.18 (3 d, $J = 7$ cps, $\alpha\text{-CH}_3$); 2.13 (3 s, 4- CH_3); 2.19 (6 d, $J = 7$ cps); 2.62-3.7 (2 m, CH_2); 3.71 (6 s, OCH_3 protons); 6.85 δ (2 s, aromatic protons)

Mass spectrum: 264 (6) [$\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_2$]; 193 (5) [$\text{C}_{12}\text{H}_{17}\text{O}_2$]; 166 (100) [$\text{C}_{10}\text{H}_{14}\text{O}_2$]; m/e (% rel. abund.)

Anal. Calc. for $\text{C}_{15}\text{H}_{25}\text{ClN}_2\text{O}_2$: C, 59.88; H, 8.38

Found: C, 59.76; H, 8.50

Catalytic hydrogenation of the isopropylhydrazone of 2,5-dimethoxy-4-methylphenylacetone hydrochloride

A solution of the isopropylhydrazone of 2,5-dimethoxy-4-methylphenylacetone hydrochloride in ethanol was hydrogenated at 50 psi and room temperature in the presence of platinum dioxide (0.05 g) for 12 hours. Removal of the catalyst and solvent left a solid residue. This residue was recrystallized from ethanol to yield colorless crystals (0.18 g), m.p. 182-185°C.

I.r. spectrum: 2550, 2700 cm^{-1} (N-H^+); absence of N=N absorption at 1660 cm^{-1}

Mass spectrum: 266 (<5) [$\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_2$]; 193 (<5) [$\text{C}_{12}\text{H}_{17}\text{O}_2$]; 166 (<5) [$\text{C}_{10}\text{H}_{14}\text{O}_2$]; m/e (% rel. abund.)

c) Reactions Related to the Synthesis of Some Substituted Phenylalanines

The azlactone of α -acetylamino-2,5-dimethoxy-4-methylcinnamic acid

A mixture of 2,5-dimethoxy-4-methylbenzaldehyde (22.0 g), acetylglycine (11.0 g), sodium acetate (6.0 g) and acetic anhydride (24 ml) was heated on a water bath until solution was attained and then heated under reflux for one hour. Cooling (5°) caused the precipitation of a solid orange mass. The product was washed with water, then filtered, leaving 17.9 g of orange solid. A small portion of the material was crystallized from benzene, m.p. $128-130^{\circ}\text{C}$. The remainder of the crude material was hydrolyzed as described below.

I.r. spectrum: 1650 (C=N) ; $1795\text{ cm}^{-1}\text{ (C=O)}$

Anal. Calc. for $\text{C}_{14}\text{H}_{15}\text{NO}$: N, 5.36

Found: N, 5.29

α -Acetylamino-2,5-dimethoxy-4-methylcinnamic acid

A solution of azlactone described above (15 g) in water (80 ml) and acetone (200 ml) was heated under reflux for four hours. The acetone was evaporated, leaving an orange solid in suspension, which was collected by filtration. The title compound crystallized from the filtrate on cooling (3.2 g). The insoluble orange solid was heated in the same acetone-water solvent for an additional ten hours, yielding another 2.1 g of the title compound.

The title compound was crystallized from ethanol-water, m.p. 205-208°C.

I.r. spectrum: 1650, 1690 (C=O); 2500-2700 (OH); 3230 cm^{-1} (NH)

N.m.r. spectrum (DMSO- d_6): 2.0 (3 s, CH_3); 2.2 (3 s, CH_2); 3.73 (3 s), 3.8 (3 s); OCH_3 protons; 6.81 (1 s), 7.26 (1 s), aromatic protons; 7.60 (1 s, CH); 9.17 δ (1 br s, OH exchanges with D_2O)

Anal. Calc. for $\text{C}_{14}\text{H}_{17}\text{NO}_5$: C, 60.20; H, 6.14;
N, 5.02

Found: C, 60.45; H, 6.60;
N, 5.36

The azlactone of α -acetylamino-2,5-dimethoxycinnamic acid

The procedure described for the preparation of the 2,5-dimethoxy-4-methyl analog was followed, using 2,5-dimethoxy-benzaldehyde (22.0 g), acetylglycine (11.0 g), and sodium acetate (6.0 g). The title compound (18.0 g) was isolated but not purified.

α -Acetylamino-2,5-dimethoxycinnamic acid

The crude azlactone above (15.0 g) was hydrolyzed by the method previously described for the hydrolysis of the azlactone of α -acetylamino-2,5-dimethoxy-4-methylcinnamic acid. A total of 9.5 g of the title material was

collected, and crystallized from ethanol, m.p. 208-209°C.

I.r. spectrum: 1655, 1695 (C=O); 2400-2600 (OH);
3250 cm^{-1} (NH)

Anal. Calc. for $\text{C}_{14}\text{H}_{15}\text{NO}_5$: C, 58.86; H, 5.70;

N, 5.28

Found: C, 59.14; H, 6.20;

N, 4.91

N-Acetyl-2,5-dimethoxy-4-methylphenylalanine

A solution of 2,5-dimethoxy-4-methyl- α -acetamido-cinnamic acid (5.0 g) in ethanol (100 ml) was hydrogenated at room temperature and 50 psi in the presence of 10% palladium-charcoal (0.5 g) until the absorption of hydrogen ceased. The catalyst was removed by filtration and the solvent was evaporated, leaving a quantitative yield of the title compound. A constant melting point of 159-160°C was attained by crystallization from ethanol.

I.r. spectrum: 1655 (amide C=O); 1710 (acid C=O);
3310 cm^{-1} (NH)

Anal. Calc. for $\text{C}_{14}\text{H}_{19}\text{NO}_5$: C, 59.77; H, 6.81;

N, 4.98

Found: C, 59.54; H, 6.73;

N, 4.89

N-Acetyl-2,5-dimethoxyphenylalanine

A solution of 2,5-dimethoxyphenyl- α -acetamidocinnamic acid (7.0 g) was similarly hydrogenated under 10% palladium-charcoal (1.0 g). The title compound was isolated in quantitative yield, m.p. 156-160°C.

I.r. spectrum: 1630 br, 1730 (C=O); 2400-2700 (OH); 3310 cm^{-1} (NH)

Anal. Calc. for $\text{C}_{13}\text{H}_{17}\text{NO}_5$: C, 58.41; H, 6.41
N, 5.24

Found: C, 58.38; H, 6.60;
N, 5.21

N-Acetyl-4-bromo-2,5-dimethoxyphenylalanine

To a stirred solution of N-acetyl-2,5-dimethoxyphenylalanine (1.0 g) in ethanol, bromine-water was added dropwise until a slight yellow color persisted. The solution was stirred for 0.5 hour, then made basic with 5% sodium bicarbonate. The solvent was removed and 5% hydrochloric acid (50 ml) was added to the residue prior to extraction with chloroform. Evaporation of the latter solvent left a red oil which did not crystallize from ethanol. A solution of the oil in 5% sodium bicarbonate was made acidic with hydrochloric acid and yielded a solid (0.62 g). Recrystallization of the solid from ethanol gave the title compound, m.p. 178-180°C.

I.r. spectrum: 1650 (amide C=O); 1730 (acid C=O);
3310 cm^{-1} (NH)

N.m.r. spectrum (DMSO-d_6): 1.79 (3 s, CH_3); 2.63-3.5
(2 m, CH_2); 3.78 (6 s, OCH_3 protons); 4.15-4.8 (1 m, CH)
7.03 (1 s), 7.18 (1 s), aromatic protons; 8.2 δ (1 d,
J = 8 cps, NH)

Anal. Calc. for $\text{C}_{13}\text{H}_{16}\text{BrNO}_5$: C, 45.10; H, 4.66;
N, 4.05

Found: C, 45.04; H, 4.73;
N, 3.81

2,5-Dimethoxy-4-methylphenylalanine hydrochloride

A suspension of N-acetyl-2,5-dimethoxy-4-methyl-
phenylalanine (4.0 g) in hydrochloric acid (60 ml) was
heated under reflux for four hours. The solvent was
evaporated under reduced pressure, leaving a light yellow
solid. After drying, the material was suspended in acetone,
then filtered, leaving the insoluble title compound (2.8 g).
This material was crystallized from ethanol, m.p. 241-242°C.

I.r. spectrum: 1580, 1950, 2410-2670 (N^+-H);
1745 cm^{-1} (C=O)

N.m.r. spectrum (DMSO-d_6): 2.18 (3 s, CH_3); 3.18
(2 d, J = 6 cps, CH_2); 3.65-4.23 (7 m, CH and OCH_3 protons);
6.84 (1 s), 7.0 (1 s), aromatic protons; 8.66 δ (4 br s,
exchanges with D_2O , NH_3 and OH protons)

Anal. Calc. for $C_{12}H_{17}ClNO_4$: C, 52.46; H, 6.24;

N, 5.10

Found: C, 52.40; H, 6.55;

N, 4.86

2,5-Dimethoxyphenylalanine hydrochloride

N-Acetyl-2,5-dimethoxyphenylalanine (2.0 g) was hydrolyzed in the same manner as described immediately above. The title compound (1.52 g) was isolated and recrystallized from ethanol-ether as a colorless solid, m.p. 225°C. Although this material has been reported, a melting point was not given⁽⁸³⁾.

I.r. spectrum: 1585, 2420-2680 ($\overset{+}{N}$ -H); 1750 cm^{-1} (C=O)

Anal. Calc. for $C_{11}H_{16}ClNO_4$: C, 50.48; H, 6.16;

N, 5.35

Found: C, 50.12; H, 6.29;

N, 5.35

4-Bromo-2,5-dimethoxyphenylalanine hydrochloride

N-Acetyl-4-bromo-2,5-dimethoxyphenylalanine (0.5g) was also hydrolyzed with hydrochloric acid as previously described on page 217, yielding 0.41 g of the title compound. It was crystallized from ethanol-acetone, m.p. 252-253°C.

I.r. spectrum: 1590, 2420-2680 ($\overset{+}{N}$ -H); 1735 cm^{-1} (C=O)

Anal. Calc. for $C_{11}H_{15}BrClNO_4$: C, 38.79; H, 4.44;

N, 4.11

Found: C, 39.07; H, 4.62;
N, 4.11

Attempted preparation of 2,5-dihydroxy-4-methylphenylalanine hydrochloride

A solution of 2,5-dimethoxy-4-methylphenylalanine hydrochloride (2.0 g) in 50% hydriodic acid (10 ml) was heated under reflux for two hours. Evaporation of the solvent left a red oily residue. The oil was dissolved in acetone and, on cooling, a yellow solid (0.2 g) formed. Crystallization of this material from ethanol-ether proved unsuccessful. A large excess of ether did not facilitate crystallization after standing several weeks. The solvent was then evaporated, leaving a dark brown oil. Addition of water to the residue resulted in the formation of an insoluble suspension. This material was removed by filtration and the aqueous solution was evaporated, leaving a brown-red oil. Further attempts to crystallize the oil from ethanol-ether were again unsuccessful, as were attempts to find the isoelectric point of the amino acid by slowly altering the pH of an aqueous solution of the oil.

The azlactone of α -benzoylamino-2,5-dimethoxy-4-methylcinnamic acid

A mixture of 2,5-dimethoxy-4-methylbenzaldehyde (15.0 g), hippuric acid (15.0 g), acetic anhydride (26.0 g), and anhydrous sodium acetate (7.0 g) was heated on a hot

plate with constant stirring. When complete liquifaction occurred, the solution was heated on a steam bath for two hours, then ethanol (100 ml) was added. The heavy precipitate which formed on cooling was collected (23.6 g), then washed with water. A small amount of the material was crystallized from benzene, m.p. 208-210.5°C.

I.r. spectrum: 1645 (C=N); 1785 cm^{-1} (C=O)

Anal. Calc. for $\text{C}_{19}\text{H}_{17}\text{NO}_4$: N, 4.33

Found: N, 4.22

Cleavage of the azlactone of α -benzoylamino-2,5-dimethoxy-4-methylcinnamic acid with red phosphorus and hydriodic acid

To the crude azlactone prepared above (21.0 g) and red phosphorus (18.0 g) in acetic anhydride (60 ml) was added 50% hydriodic acid (60 ml) over one hour. The reaction mixture was heated under reflux for three hours, cooled, and then filtered. The solvent was removed under reduced pressure, leaving a semi-solid residue. Water (100 ml) was added to the residue and the resulting suspension was extracted several times with ether. The ether extracts were discarded. An interfacial solid was collected by filtration. Although the filtrate was positive to ninhydrin reagent, attempts to find the isoelectric point by slowly altering the pH of the cooled solution with ammonium hydroxide and hydrochloric acid were unsuccessful. The interfacial material (3.1 g), m.p. 262-264°C (from

ethanol) was the azlactone of α -benzoylamino- β -(2,5-dihydroxy-4-methylphenyl)propionic acid.

I.r. spectrum: 1642 (C=N); 1765 (C=O); 3300 br; 3440 cm^{-1} (OH)

Mass spectrum: 297 (8) [$\text{C}_{17}\text{H}_{15}\text{NO}_4$];
m/e (% rel. abund.)

Anal. Calc. for $\text{C}_{17}\text{H}_{15}\text{NO}_4$: C, 68.67; H, 5.09;
N, 4.71

Found: C, 68.41; H, 5.51;
N, 4.48

The reaction described immediately above was repeated with 13.0 g of azlactone except the reaction mixture was heated under reflux for five hours. After filtering and extracting with ether, the aqueous solution was evaporated under reduced pressure, leaving a brown oil. This oil was dissolved in water, then filtered. Dilute ammonium hydroxide was slowly added until the solution attained a pH of 4-5. This caused the precipitation of a solid (3.2 g), m.p. 250-300°C (decomp.). A solution of this material turned blue when treated with ninhydrin reagent. A solution of the solid in 10% hydrochloric acid was evaporated to dryness. Crystallization of the resulting oily residue from ethanol and ether yielded the lactone of 2,5-dihydroxy-4-methylphenylalanine hydrochloride, m.p. 255-257°C.

I.r. spectrum: 1765 (C=O); 2450-2650 (N^+-H);
3120 br, 3300 cm^{-1} (OH)

N.m.r. spectrum (DMSO d_6): 2.13 (3 s, CH_3); 3.27 (2 d, $J = 10$ cps, CH_2); 4.57 (1 t, $J = 10$ cps, CH);, 6.85 (1 s), 6.93 (1 s), aromatic protons; 7.4-10.7 δ (3, 2 br s, NH_2^+ and/or OH, exchanges with D_2O).

Mass spectrum: 193 (11) [$\text{C}_{10}\text{H}_{11}\text{NO}_3$]; 165 (80) [$\text{C}_9\text{H}_{11}\text{NO}_2$]; 148 (18) [$\text{C}_9\text{H}_{10}\text{NO}$]; 138 (22) [$\text{C}_8\text{H}_{10}\text{O}_2$];
m/e (% rel. abund.)

Accurate mass determinations: 193.0732, $\text{C}_{10}\text{H}_{11}\text{NO}_3$ requires 193.0739; 165.0786, $\text{C}_9\text{H}_{11}\text{NO}_2$ requires 165.0790; 148.0758, $\text{C}_9\text{H}_{10}\text{NO}$ requires 148.0762

Anal. Calc. for $\text{C}_{10}\text{H}_{12}\text{ClNO}_3$: C, 52.29; H, 5.27;
N, 6.10

Found: C, 48.81; H, 5.96;
N, 5.44

Anal. Calc. for $\text{C}_{10}\text{H}_{12}\text{ClNO}_3 \cdot \text{H}_2\text{O}$: C, 48.49; H, 5.70;
N, 5.66

d) Reactions Related to the Synthesis of Some Possible Metabolites of 1-(2,5-Dimethoxy-4-methylphenyl)isopropylamine) (DOM)

Methyl 2,5-dimethoxy-4-methylphenylacetate

A solution of the azlactone of α -benzoylamino-2,5-dimethoxy-4-methylcinnamic acid (15.0 g) in 10% sodium hydroxide (100 ml) was heated under reflux for 12 hours. After this period of time, an additional 10 ml of 40% sodium hydroxide was added to the reaction mixture which was then cooled in an ice-salt mixture. With stirring,

30% hydrogen peroxide (10 ml) diluted with water (10 ml) was added at such a rate as to maintain the temperature below 15°. After standing for 12 hours at room temperature the solution was acidified by the careful addition of concentrated hydrochloric acid (50 ml). The solution was extracted with benzene (200 ml), then dried over magnesium sulfate. The benzene was evaporated, leaving a solid (20.5 g) which was dissolved in methanol (100 ml) and sulfuric acid (2 ml), then heated under reflux for five hours. The methanol was evaporated to give an oil which solidified on cooling (9.2 g). Crystallization from ethanol gave the title compound, m.p. 66-67°C.

I.r. spectrum: 1730 cm^{-1} (C=O)

N.m.r. spectrum (CDCl_3): 2.21 (3 s, 4- CH_3); 3.60-3.77 (11 m, CH_2 , CH_3 and OCH_3 protons); 6.72 δ (2 s, aromatic protons)

Anal. Calc. for $\text{C}_{12}\text{H}_{16}\text{O}_4$: C, 64.27; H, 7.19

Found: C, 63.96; H, 7.29

2,5-Dimethoxy-4-methylphenylacetic acid

A suspension of methyl 2,5-dimethoxy-4-methylphenylacetate (8.0 g) in 10% sodium hydroxide (50 ml) was heated under reflux for one hour, cooled, and acidified with hydrochloric acid. The resulting precipitate (7.6 g) was collected, washed with cold water, then crystallized from ethanol to yield the title compound, m.p. 128-129.3°C.

I.r. spectrum: 1700 br (C=O); 2500-2700 cm^{-1} (OH)

N.m.r. spectrum (CDCl_3): 2.2 (3 s, CH_3); 3.60 (3 s, CH_2); 3.73 (6 s, OCH_3 protons); 6.7 (2 s, aromatic protons); 10.8 δ (1 s, exchanges with D_2O , OH)

Anal. Calc. for $\text{C}_{11}\text{H}_{14}\text{O}_4$: C, 62.84; H, 6.71

Found: C, 62.60; H, 6.83

2,5-Dimethoxy-4-methylphenylacetone

A solution of 2.1M methyllithium (Alfa Inorganic, Inc.) (40 ml) was slowly added to 2,5-dimethoxy-4-methylphenylacetic acid (6.3 g) in sodium dried ether (300 ml). When the addition was completed, a saturated solution of ammonium chloride (150 ml) was carefully added to the reaction mixture. The ether layer was separated and the aqueous layer extracted with ether (150 ml). The ether solutions were combined, washed with water, and then dried over magnesium sulfate. Evaporation of the solvent left a brown oil which was positive to 2,4-DNP reagent. The oil solidified, yielding 3.1 g of the title compound, m.p. 56-58°C (from ethanol). Reported m.p. 49-51°C⁽¹⁰¹⁾.

I.r. spectrum: 1710 cm^{-1} (C=O)

N.m.r. spectrum (CDCl_3): 2.13 (3 s, acetyl protons); 2.23 (3 s, 4- CH_3); 3.65 (2 s, CH_2); 3.78 (6 s, OCH_3 protons); 6.63 (1 s), 6.72 δ (1 s), aromatic protons

Mass spectrum: 208 (41) [$\text{C}_{12}\text{H}_{16}\text{O}_3$]; 165 (100) [$\text{C}_{10}\text{H}_{13}\text{O}_2$]; m/e (% rel. abund.)

Anal. Calc. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75

Found: C, 69.53; H, 7.57

The above reaction was repeated with 15.0 g of the phenylacetic acid in 400 ml of sodium dried ether and 80 ml of the methyllithium solution. Only 2 g of the product was isolated from the ether. Acidification of the aqueous portion yielded the starting acid (9.6 g).

The reaction was modified so that the acid (9.0 g) in ether (300 ml) was added to the solution of methyl-lithium (60 ml). The mixture was heated under reflux for one hour, then added to an ice-water solution saturated with ammonium chloride (200 ml). The organic layer was collected and the aqueous portion was extracted with ether (200 ml). Evaporation of the combined ether portions yielded the ketone (4.7 g). Acidification of the aqueous layer caused the precipitation of starting material (2.1 g).

2,5-Dimethoxy-4-methylphenylacetone oxime

A solution of 2,5-dimethoxy-4-methylphenylacetone (1.0 g), hydroxylamine hydrochloride (1.0 g) in ethanol (10 ml) and pyridine (5 ml) was heated under reflux for one hour, then evaporated. The residue was suspended in 5% hydrochloric acid (25 ml) and extracted with chloroform. Evaporation of this extract yielded a light yellow oil (1.1 g).

I.r. spectrum: 1660 (C=O) was absent;
3300 cm^{-1} br (OH)

A solution of this oil in ether (50 ml) was saturated with gaseous hydrogen chloride. A crystalline solid slowly formed. Successive crops of crystals of the hydrochloride salt of the title compound (0.64 g) were collected, m.p. 114-117°C.

I.r. spectrum: 2500 cm^{-1} ($\text{N}^+\text{-H}$)

Mass spectrum: 223 (100) [$\text{C}_{12}\text{H}_{17}\text{NO}_3$]; 192 (98) [$\text{C}_{11}\text{H}_{14}\text{NO}_2$]; 176 (25) [$\text{C}_{11}\text{H}_{14}\text{NO}$]; 175 (30) [$\text{C}_{11}\text{H}_{13}\text{NO}$];
m/e (% rel. abund.)

Accurate mass determinations: 223.1199, $\text{C}_{12}\text{H}_{17}\text{NO}_3$ requires 223.1208; 192.1025, $\text{C}_{11}\text{H}_{14}\text{NO}_2$ requires 192.1020; 176.1075, $\text{C}_{11}\text{H}_{14}\text{NO}$ requires 176.1067; 175.0997, $\text{C}_{11}\text{H}_{13}\text{NO}$ requires 175.0993

N.m.r. spectrum (CDCl_3): 2.04 (3 s, CH_3); 2.24 (3 s, 4- CH_3); 3.66-3.95 (8 m, CH_2 and OCH_3 protons); 6.73 (1 s), 6.8 (1 s), aromatic protons; 13.08 δ (2 br s, N^+HOH)

Anal. Calc. for $\text{C}_{12}\text{H}_{18}\text{ClNO}_3$: C, 55.49; H, 6.98;
N, 5.39

Found: C, 55.47; H, 6.91;
N, 5.59

1-(2,5-Dimethoxy-4-methylphenyl)-2-propanol

A solution of 2,5-dimethoxy-4-methylphenylacetone (2.0 g) in ethanol (100 ml) was hydrogenated for 24 hours

at normal temperature and pressure under platinum oxide (0.05 g) or 10% palladium-charcoal (0.1 g), but the compound failed to absorb any hydrogen. A quantitative yield of starting material was recovered.

A solution of 2,5-dimethoxy-4-methylphenylacetone (2.0 g) in methanol (30 ml) was slowly added to a stirred solution of sodium borohydride (2.0 g) in methanol (200 ml) and water (100 ml). After one hour, hydrochloric acid was carefully added to the reaction mixture until effervescence stopped. The solvent was removed under reduced pressure. The residue which remained was suspended in water (100 ml) and extracted with chloroform (200 ml). When this latter solvent was evaporated, the title compound remained (1.2 g). It was crystallized from ethanol, m.p. 80.5-81.5°C.

I.r. spectrum: $3100-3500\text{ cm}^{-1}$ (OH)

N.m.r. spectrum (DMSO- d_6): 1.0 (3 d, $J = 6$ cps, $\alpha\text{-CH}_3$); 2.12 (3 s, 4- CH_3); 2.65 [1 m (overlaps with DMSO CH)]; 3.6-4.27 (8 m, CH_2 and OCH_3 protons); 4.27 (1 br s, exchanges with D_2O , OH); 6.72 δ (2 s, aromatic protons)

Anal. Calc. for $\text{C}_{12}\text{H}_{18}\text{O}_3$: C, 68.54; H, 8.63

Found: C, 68.62; H, 8.73

N-Acetyl-1-(2,5-dimethoxy-4-methylphenyl)isopropylamine

A solution of 1-(2,5-dimethoxy-4-methylphenyl)isopropylamine hydrochloride (DOM) (1.0 g) in water (10 ml) and acetic anhydride (10 ml) was shaken vigorously until

the evolution of heat subsided. Sodium acetate (10.0 g) in water (10 ml) was added to the reaction mixture in one portion; the solution was then cooled. A precipitate of the title compound (0.61 g) was collected by filtration. Crystallization from ethanol afforded a constant melting point of 144-145°C. Reported m.p. 144-145°C⁽¹⁰¹⁾.

I.r. spectrum: 1650 (C=O); 3310 cm^{-1} (NH)

e) Examination of Some of the Side Products in a Synthesis of 1-(2,5-Dimethoxy-4-methylphenyl)isopropylamine (DOM)

1-(2,5-Dimethoxy-4-methylphenyl)-2-nitropropene-1

A solution of 2,5-dimethoxy-4-methylbenzaldehyde (15.0 g) and ammonium acetate (6.3 g) in acetic acid (75 ml) and nitroethane (9.9 g) was heated on a water bath or heated under gentle reflux for three hours. The dark red solution was evaporated, leaving a red oil. This residue was suspended in water (100 ml) and extracted with chloroform. Evaporation of this solvent left an oil which turned to a yellow solid. The solid (14.4 g) was crystallized from ethanol to yield the title compound, m.p. 85-87°C. Reported m.p. 85.5-87.5°C⁽¹⁷⁵⁾.

I.r. spectrum: 1320, 1500 (NO_2); 1645 cm^{-1} (C=C)

N.m.r. spectrum (CDCl_3): 2.24 (3 s, 4- CH_3); 2.40 (3 s, α - CH_3); 3.80 (3 s), 3.82 (3 s), OCH_3 protons; 6.70 (2 s, aromatic protons); 8.3 δ (1 s, CH)

Anal. Calc. for $\text{C}_{12}\text{H}_{15}\text{NO}_4$: C, 60.75; H, 6.37

Found: C, 61.04; H, 6.36

Catalytic hydrogenation of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene-1

A solution of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene-1 (7.5 g) in ethanol (300 ml) was hydrogenated at room temperature and pressure in the presence of palladium-charcoal (1.0 g). When the reaction flask was removed from the hydrogenation apparatus, the pungent odor of ammonia was evident. Moistened red litmus paper when held above the reaction flask, turned blue. The solution was stirred for three hours, then hydrogenated further. Hydrogen was incorporated slowly. After the uptake of hydrogen ceased, the catalyst was removed and the solvent evaporated. An oil which was positive to 2,4-DNP reagent remained.

I.r. spectrum: 1350, 1550 (NO_2); 1710 (C=O); 3300 cm^{-1} br (OH)

The oil was then dissolved in chloroform and extracted with 5% hydrochloric acid. The aqueous solution was basified with sodium hydroxide and extracted with chloroform. This extract was then saturated with gaseous hydrogen chloride. The solvent was evaporated and the residue was fractionally crystallized from ethanol and ether. Two compounds were isolated. The first was found, by i.r. spectral comparisons and mixed melting point determinations, to be DOM. The other product (0.8 g) was found to be N-(2,5-dimethoxy- α -4-dimethylphenethyl)hydroxylamine hydrochloride, m.p. 121-213°C.

I.r. spectrum: 2480-2750 (N-H^+)

Mass spectrum: 225 (9) [$\text{C}_{12}\text{H}_{19}\text{NO}_3$]; 193 (5) [$\text{C}_{12}\text{H}_{17}\text{O}_2$]; 166 (100) [$\text{C}_{10}\text{H}_{14}\text{O}_2$]; 60 (45) [$\text{C}_2\text{H}_6\text{NO}$]; 44 (18) [$\text{C}_2\text{H}_6\text{N}$]; m/e (% rel. abund.)

Accurate mass measurements: 193.1230, $\text{C}_{12}\text{H}_{17}\text{O}_2$ requires 193.1229; 166.0991, $\text{C}_{10}\text{H}_{14}\text{O}_2$ requires 166.0994; 60.0458, $\text{C}_2\text{H}_6\text{NO}$ requires 60.0449; 44.0498, $\text{C}_2\text{H}_6\text{N}$ requires 44.0500

Anal. Calc. for $\text{C}_{12}\text{H}_{20}\text{ClNO}_3$: C, 55.06; H, 7.70;
N, 5.35

Found: C, 55.06; H, 7.81;
N, 5.51

The chloroform extract was evaporated and the oil which remained was dissolved in ether, then saturated with gaseous hydrogen chloride.

This caused the precipitation of another oil. The solvent was decanted off and the oil was dissolved in ethanol and sufficient ether to cause the solution to become foggy. On cooling, crystals separated from solution and successive crops were collected over a period of one month. This material (1.1 g) melted at 112-115°C. Mixed melting point determinations as well as i.r. spectral comparisons showed that the compound was the hydrochloride salt of the oxime of 2,5-dimethoxy-4-methylphenylacetone.

The decanted solution from which the oxime was isolated was evaporated, then distilled under reduced

pressure. A light yellow oil distilled between 110 and 160° (0.1-1.5 mm). A black oil failed to distill at temperatures up to 200° and appeared to decompose at this temperature. The oil which distilled between 110 and 160° was positive to 2,4-DNP reagent.

I.r. spectrum: 1710 cm^{-1} (C=O)

The oil was dissolved in ethanol and seeded with 2,5-dimethoxy-4-methylphenylacetone, then cooled. A solid (1.7 g) with an i.r. spectrum superimposable on 2,5-dimethoxy-4-methylphenylacetone crystallized from solution.

Catalytic hydrogenation of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene-1 in ethanol and hydrochloric acid

A solution of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene-1 (7.0 g) in ethanol (100 ml) and hydrochloric acid (7 ml) was hydrogenated at room temperature and pressure in the presence of palladium-charcoal (1.0 g). Hydrogen was rapidly incorporated over several hours. After the uptake of hydrogen ceased, the catalyst was removed and the solvent evaporated. The oil which remained was dissolved in chloroform (100 ml) and extracted with 5% hydrochloric acid (25 ml). This latter solvent was evaporated, leaving a solid (0.46 g). This material was dissolved in ether and saturated with hydrogen chloride gas. The resulting precipitate had an i.r. spectrum virtually superimposable on the i.r. spectrum of 1-(2,5-di-

methoxy-4-methylphenyl)isopropylamine hydrochloride.

The chloroform solution from which the basic material was isolated was evaporated, leaving a red oil (5.4 g).

I.r. spectrum: 1710 (C=O); 2500 cm^{-1} br ($\text{N}^+\text{-H}$)

This oil was dissolved in acetone, then ether was added until the solution became foggy. Successive crops of crystals were collected over a period of several weeks (3.3 g). This material had an i.r. spectrum superimposable on the i.r. spectrum of the hydrochloride salt of the oxime of 2,5-dimethoxy-4-methylphenylacetone.

Evaporation of the filtrate left an oil.

I.r. spectrum: 1710 (C=O); 2500 cm^{-1} br ($\text{N}^+\text{-H}$)

This material was not investigated further.

Catalytic hydrogenation of crude 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene-1

1-(2,5-Dimethoxy-4-methylphenyl)-2-nitropropene-1 was prepared as described on page 228.

I.r. spectrum: 1320, 1500 (NO_2); 2210 cm^{-1} ($\text{C}\equiv\text{N}$)

This crude material (7.0 g) was dissolved in ethanol (100 ml) and hydrochloric acid (10 ml), then hydrogenated at room temperature and pressure in the presence of palladium-charcoal (0.7 g). Hydrogen was incorporated rapidly for two hours, then slowly absorbed over approximately 12 hours. The catalyst was removed and the solvent evaporated. The oil which remained was dissolved in ethanol and ether and allowed to crystallize.

Successive crops of a solid were collected (0.8 g).
Recrystallization of this material from ethanol and ether
yielded 2,5-dimethoxy-4-methylbenzylamine hydrochloride,
m.p. 245°C.

I.r. spectrum: 1600, 2010, 2600-2700 cm^{-1} (N^+-H)

Mass spectrum: 181 (90) [$\text{C}_{10}\text{H}_{15}\text{NO}_2$];
m/e (% rel. abund.)

N.m.r. spectrum ($\text{DMSO}-d_6$): 2.16 (3 s, CH_3);
1.9 (1 s ?); 3.78 (6 s, OCH_3 protons); 3.96 (2 s, CH_2);
6.9 (1 s), 7.23 (1 s), aromatic protons; 8.0-8.83 δ (3 br s,
exchanges with D_2O , NH_3^+)

Anal. Calc. for $\text{C}_{10}\text{H}_{16}\text{ClNO}_2$: N, 6.44

Found: N, 6.60

Also collected from the above reaction mixture was
the hydrochloride salt of the oxime of 2,5-dimethoxy-4-
methylphenylacetone.

2,5-Dimethoxy-4-methylbenzonitrile

Fractional crystallization of 5 g of the crude
nitropropene (page 232) from ethanol yielded 2,5-dimethoxy-
4-methylbenzonitrile (0.6 g), m.p. 127-129°C.

I.r. spectrum: 2210 cm^{-1} ($\text{C}\equiv\text{N}$)

N.m.r. spectrum (CDCl_3): 2.33 (3 s, CH_3); 3.86 (3 s),
3.93 (3 s), OCH_3 protons; 6.87 (1 s), 6.96 δ (1 s),
aromatic protons

Anal. Calc. for $C_{10}H_{11}NO$: C, 67.77; H, 6.26;
N, 7.91

Found: C, 67.82; H, 6.36;
N, 7.48

Reaction of 2,5-dimethoxy-4-methylbenzaldehyde, acetic acid and ammonium acetate in the absence of nitroethane

A solution of 2,5-dimethoxy-4-methylbenzaldehyde (5.0 g) and ammonium acetate (2.1 g) in acetic acid (25 ml) was heated under reflux for three hours. Evaporation of the solvent left an oil.

I.r. spectrum: 2250 cm^{-1} was not present

Reaction of 3,4-methylenedioxybenzaldehyde with nitroethane

A solution of 3,4-methylenedioxybenzaldehyde (10 g) and ammonium acetate (5.0 g) in acetic acid (100 ml) and nitroethane (5.0 g) was heated under reflux for three hours. The reaction mixture was poured into cold water (300 ml) and extracted with chloroform (200 ml). Evaporation of this solvent left a red oil which was positive to 2,4-DNP reagent.

I.r. spectrum: 1690 (C=O) ; $2210\text{ cm}^{-1}\text{ (C}\equiv\text{N)}$

The oil was distilled under reduced pressure and the following fractions were collected: (a) $92-102^\circ$ (0.1 mm); (b) $102-112^\circ$ (0.1 mm); (c) $116-130^\circ$ (0.2-0.5 mm); and (d) $150-170^\circ$ (2.0-3.0 mm). The i.r. spectra of

fractions (a)-(c) were superimposable, and these fractions were combined.

I.r. spectrum: 1690 (C=O); 2210 cm^{-1} (C $\equiv$ N)

Fraction (d) solidified and was crystallized from ethanol to yield 1-(3,4-methylenedioxyphenyl)-2-nitropropene-1 (3.6 g), m.p. 91-93°C. Reported m.p. 86-87°C⁽²¹¹⁾.

I.r. spectrum: 1640 (C=C); 1370, 1515 cm^{-1} (NO₂)

The combined (a)-(c) fractions (5.1 g) in ether (100 ml) were added to a stirred suspension of lithium aluminum hydride (2.5 g) in the same solvent (100 ml). The mixture was heated under reflux for three hours. The excess lithium aluminum hydride was then decomposed by the careful addition of water. The thick suspension was filtered and the insoluble cake washed thoroughly with ether. The combined ether fractions were evaporated and the residue was dissolved in chloroform (50 ml) and extracted with 5% hydrochloric acid (50 ml). This latter solvent was basified with sodium hydroxide, then extracted with chloroform. The oil which remained after evaporation of the chloroform was dissolved in ether and saturated with hydrogen chloride gas. The precipitate (0.6 g) was crystallized from ethanol and acetone to yield 3,4-methylenedioxybenzylamine hydrochloride, m.p. 242°C. Reported m.p. 242°C⁽²¹²⁾; m.p. 238-240°C⁽²¹³⁾; m.p. 225°C⁽²¹⁴⁾.

I.r. spectrum: 1600, 2050, 2550-2700 cm^{-1} (N-H⁺)

g) Experiments Related to the Analysis of Some 'Street' STP

Sample form

Two different samples of police seized STP were obtained from the Food and Drug Directorate, Ottawa.

Sample A consisted of light yellow tablets, which were spotted with orange and blue-brown particles. Each tablet was cylindrical, with a diameter of 5 mm and a height of 2 mm. The average weight of a tablet was 0.117 g. The source of this sample of STP was Nanaimo, B.C. Ref. 321-53A-T.

Sample B consisted of brown speckled, pale yellow elongated biconvex tablets. They had a length of 1.6 cm and a width of 0.8 cm. The average weight of a tablet was 0.301 g. The source of this sample of STP was Winnipeg, Manitoba. Ref. 327-K-541.

Extraction procedure

Two crushed and powdered tablets were triturated with 1% tartaric acid (0.5 ml) in a 30 ml beaker. To this mixture was added chloroform (1 ml) and sodium bicarbonate (1.0 g) and mixed well. Without delay celite 545 (1.0 g) was uniformly incorporated into the mixture. The mixture was then put in a 13 X 100 mm glass column (drawn out glass tube) with a pledget of glass wool on the bottom. The beaker was then scrubbed with dry celite (0.5 g) which was added to the column. A pledget of glass wool was placed

at the top of the column and prepurified chloroform (15 ml) was passed through the mixture.

The chloroform was then extracted with 2 X 1 ml portions of 0.1N sulfuric acid. This extract was transferred to a 5 ml centrifuge tube, then basified with concentrated ammonia (10 drops). After chloroform (8.0 ml) was added, the mixture was shaken well and centrifuged. The chloroform layer was drawn off with a syringe and the extraction procedure was repeated with an additional 8 ml of chloroform. The combined extracts were then dried under a stream of nitrogen on a water bath. The dried basic extract of sample A weighed 3.5 mg and the neutral portion weighed 44 mg. The basic extract of sample B weighed 3.0 mg and the neutral portion weighed 57 mg.

Accurate mass spectral measurements:

a) basic extract of sample A

193.1210, $C_{10}H_{15}N_3O$ requires 193.1215; 192.1143, $C_{10}H_{14}N_3O$ requires 192.1137

b) basic extract of sample B

265.1663, $C_{15}H_{23}NO_3$ requires 265.1678

Thin-layer chromatography

Glass plates 20 cm X 20 cm were coated with 250 μ of silica gel containing 0.1N sodium hydroxide. The plates were activated at 110°C for one hour prior to their use.

The basic and neutral extracts of samples A and B

and the reference compounds, DOM (Dow Chemical), N-(2,5-dimethoxy- α ,4-dimethylphenethyl)hydroxylamine, 2,5-dimethoxy-4-methylbenzylamine, 2,5-dimethoxy-4-methylphenylacetone, 2,5-dimethoxy-4-methylphenylacetone oxime, were chromatographed under identical conditions employing the following four solvent systems:

- 1) n-hexane - ethyl acetate - methanol (70:130:50)
- 2) chloroform - methanol - acetic acid (75:20:5)
- 3) butanol
- 4) methanol - water (95:5)

The plates were dried, visualized under ordinary and ultraviolet light, and then sprayed with 1% 2,4-dinitrophenylhydrazine in ethanol. Comparison of the spots under these conditions showed that none of the reference materials except DOM were present in either of the extracts of samples A and B. More than one basic component was observed to be present in both the basic extracts of STP.

II. THE PREPARATION OF AMINOINDANES AND RELATED COMPOUNDS

a) Reactions Related to the Synthesis of 2-Amino-4,7-dimethoxy-5-methylindane and Related Compounds

2,5-Dimethoxy-4-methylcinnamic acid

A solution of 2,5-dimethoxy-4-methylbenzaldehyde (9.2 g), malonic acid (12.0 g), dry pyridine (24 ml) and piperidine (0.6 ml) was heated on a steam bath for three hours. The clear yellow solution was then added to hydrochloric acid (35 ml) and ice (60.0 g). The resulting copious yellow precipitate was filtered and then washed with 5% hydrochloric acid. Crystallization from ethanol yielded the title compound (11.4 g), m.p. 158-161°C.

I.r. spectrum: 1618 (C=C); 1690 (C=O);
2500-2700 cm^{-1} (OH)

N.m.r. spectrum (CDCl_3): 2.23 (3 s, CH_3); 3.81 (3 s), 3.83 (3 s), OCH_3 protons; 6.5 (1 d, $J = 17$ cps, $\alpha\text{-CH}$); 6.75 (1 s), 6.96 (1 s), aromatic protons; 8.12 (1 d, $J = 17$ cps, $\beta\text{-CH}$); 10.66 δ (1 br s, exchanges with D_2O , OH)

Anal. Calc. for $\text{C}_{12}\text{H}_{14}\text{O}_4$: C, 64.85; H, 6.35

Found: C, 64.95; H, 6.46

3-(2,5-Dimethoxy-4-methylphenyl)propionic acid

A solution of 2,5-dimethoxy-4-methylcinnamic acid (10.0 g) in ethanol was hydrogenated at room temperature and pressure under 10% palladium-charcoal (0.5 g). When

the theoretical volume of hydrogen was absorbed, the catalyst was removed by filtration and the filtrate was evaporated, leaving a quantitative yield of the title compound. Crystallization from ethanol achieved a constant melting point of 108-110°C.

I.r. spectrum: 1700 (C=O); 2500-2700 cm^{-1} (OH)

Anal. Calc. for $\text{C}_{12}\text{H}_{16}\text{O}_4$: C, 64.27; H, 7.19

Found: C, 64.02; H, 7.19

Preparation of 4,7-dimethoxy-6-methyl-1-indanone by cyclization of 3-(2,5-dimethoxy-4-methylphenyl)propionic acid with:

a) phosphorus oxychloride

A solution of 3-(2,5-dimethoxy-4-methylphenyl)propionic acid (6.0 g) in 1,1,2,2-tetrachloroethane (120 ml) and phosphorus oxychloride (6 ml) was heated under reflux for three hours. The solvent was evaporated and 5% sodium hydroxide was added to the residue prior to extraction with chloroform. Evaporation of the organic solvent left a black semi-solid mass, which crystallized from ethanol over an extended period of time (3.95 g). Recrystallization from ethanol afforded the title compound, m.p. 104-105.5°C.

I.r. spectrum: 1710 cm^{-1} (C=O)

N.m.r. spectrum (DMSO-d_6): 2.21 (3 s, CH_3); 2.35-3.07 (4 m, CH_2 protons); 3.73 (3 s), 3.80 (3 s), OCH_3 protons; 7.07 δ (1 s, aromatic proton)

Anal. Calc. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84

Found: C, 69.78; H, 6.94

b) polyphosphoric acid

(i) Powdered 3-(2,5-dimethoxy-4-methylphenyl)propionic acid (10.0 g) was added to polyphosphoric acid (100.0 g) and stirred with a spatula until a uniform mixture was obtained. The reaction turned a light yellow color and was allowed to stand one hour at room temperature. The viscous mixture was then poured into ice water (300 ml). The resulting precipitate was collected by filtration and washed with water. A solution resulted when this compound was stirred with 5% sodium bicarbonate, indicating that starting material had been recovered.

(ii) 3-(2,5-Dimethoxy-4-methylphenyl)propionic acid (1.0 g) was heated and stirred with polyphosphoric acid (10.0 g) at 60° for 25 minutes. This caused the reaction mixture to turn dark yellow. Treatment of the reaction mixture as described immediately above yielded 0.75 g of 4,7-dimethoxy-6-methyl-1-indanone.

Similarly, heating 3-(2,5-dimethoxy-4-methylphenyl)propionic acid (10.0 g) in polyphosphoric acid (100 g) at 80° for 1.5 hours yielded 6.8 g of the cyclized product.

Preparation of ethyl nitrite

Two solutions were prepared. Solution A consisted of sodium nitrite (31.0 g), ethanol (15 ml) and sufficient

water to make a total volume of 150 ml. Solution B contained sulfuric acid (13 ml), alcohol (15 ml) and water sufficient to make a total volume of 150 ml. Ethyl nitrite was generated continuously in gaseous form by allowing solution B to flow into solution A. An appropriate apparatus was used to permit and control gas formation.

4,7-Dimethoxy-2-isonitroso-6-methyl-1-indanone

Ethyl nitrite was generated at a rate such that a steady flow of gas passed through a solution of 4,7-dimethoxy-6-methyl-1-indanone (11.0 g) in ethanol (100 ml) previously saturated with hydrogen chloride gas. The stirred solution was kept at 35°. After approximately 0.5 hour a crystalline material separated from solution. This solid was removed by filtration. The filtrate was further saturated with ethyl nitrite, and additional crops were collected. After a total of two hours, the generation of gas was stopped and the solution was stoppered and cooled overnight, to yield an additional small amount of solid material.

The solids were combined (6.8 g) and dissolved in 10% sodium hydroxide (50 ml), then filtered. Acidification of the filtrate with hydrochloric acid gave the title compound, m.p. 219-220°C.

I.r. spectrum: 1645 (C=N); 1730 (C=O); 3280 cm^{-1} br

Anal. Calc. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57;
N, 5.96

Found: C, 61.07; H, 5.46;
N, 5.72

Hydrogenation of 4,7-dimethoxy-2-isonitroso-6-methyl-1-indanone in the presence of palladium-charcoal

A suspension of 4,7-dimethoxy-2-isonitroso-6-methyl-1-indanone (3.0 g) in glacial acetic acid (100 ml) was hydrogenated at room temperature and pressure under 10% palladium-charcoal (0.15 g). When the incorporation of hydrogen ceased, the catalyst was removed by filtration, and the solvent was evaporated, leaving a black oily residue. A 5% sodium bicarbonate solution (50 ml) was added to the residue, then extracted with chloroform. Saturation of the chloroform extract with hydrogen chloride gas followed by evaporation left a black oil which was not water soluble. Attempted crystallization from ethanol was unsuccessful, and further investigation was discontinued.

A suspension of 4,7-dimethoxy-2-isonitroso-6-methyl-1-indanone (2.0 g) in ethanol (200 ml) was subjected to hydrogenation at room temperature and pressure in the presence of 10% palladium-charcoal (0.2 g). When incorporation of hydrogen was complete, the catalyst was removed by filtration, leaving a clear colorless liquid which slowly turned red. Addition of concentrated hydrochloric acid (3 ml) decolorized the solution and further reddening was

not observed. Removal of the solvent left a white solid (1.8 g). Crystallization from ethanol-ether yielded 2-amino-4,7-dimethoxy-1-indanone hydrochloride, m.p. 247-252°C. Isolation of the same product was more easily accomplished by hydrogenating the starting material in 200 ml of ethanol and 5 ml of hydrochloric acid.

I.r. spectrum: 1600, 1980, 2450-2630 (N-H^+);
1720 cm^{-1} (C=O)

N.m.r. spectrum (D_2O): 2.33 (3 s, CH_3); 2.5-3.7 (2 m, CH_2); 3.87 (3 s), 3.95 (3 s), OCH_3 protons; 4.15-4.57 (1 m, CH); 7.3 δ (1 s, aromatic proton)

Anal. Calc. for $\text{C}_{12}\text{H}_{16}\text{ClNO}_3$: C, 55.92; H, 6.26;

N, 5.44

Found: C, 55.09; H, 6.40;

N, 6.60

2-Amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride

(i) A solution of 2-amino-4,7-dimethoxy-6-methyl-1-indanone hydrochloride (5.0 g) in methanol (50 ml) and water (50 ml) was added dropwise to a stirred solution of sodium borohydride (5.0 g) in methanol (50 ml) and water (50 ml). The solution was stirred three hours, then acidified with hydrochloric acid. The methanol was evaporated and the remaining suspension was extracted with chloroform. Evaporation of the chloroform yielded the title compound (2.4 g), m.p. 166-168°C (ethanol).

The hydrochloride salt was prepared by saturating a solution of the base in chloroform with gaseous hydrogen chloride. The solvent was then evaporated and the title compound recrystallized from ethanol-ether, m.p. 194-195°C.

I.r. spectrum: 1610, 2000, 2420-2650 ($\overset{+}{N}$ -H);
3350 cm^{-1} (OH)

Mass spectrum: 223 (95) [$\text{C}_{12}\text{H}_{17}\text{NO}_3$];
m/e (% rel. abund.)

Anal. Calc. for $\text{C}_{12}\text{H}_{18}\text{ClNO}_3$: C, 55.49; H, 6.98;
N, 5.39

Found: C, 55.23; H, 7.16;
N, 5.50

(ii) A solution of 4,7-dimethoxy-2-isonitroso-6-methyl-1-indanone (10.0 g) in ethanol (100 ml) and sufficient 10% sodium hydroxide to attain solution of the solid was hydrogenated at room temperature and pressure in the presence of 10% palladium-charcoal (1.0 g). When the absorption of hydrogen ceased, the catalyst was removed by filtration and the solvent evaporated under reduced pressure. Water (150 ml) was added to the residue prior to extraction with chloroform. This extract was washed with water, then saturated with gaseous hydrogen chloride. Evaporation of the chloroform left a white solid (6.92 g). It was crystallized from ethanol and melted between 189-190°C. A mixed melting point determination with the 2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride prepared by

method (i) was undepressed.

4,7-Dimethoxy-5-methyl-2-indanone

A solution of 2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride (1.0 g) in hydrochloric acid (20 ml) and water (10 ml) was heated under reflux. After approximately ten minutes, a yellow oil separated from the solution. The reaction mixture was cooled, then extracted with chloroform. This procedure was repeated until evaporation of the chloroform extract failed to provide any residue. A total of 0.56 g of chloroform soluble material was isolated. Crystallization from ethanol yielded the title compound, m.p. 100-102°C. Similar yields (0.42 g) were isolated by steam distilling the reaction mixture.

I.r. spectrum: 1750 cm^{-1} (C=O)

N.m.r. spectrum (CDCl_3): 2.3 (3 s, CH_3); 3.4 (2 s), 3.5 (2 s), CH_2 protons; 3.71 (3 s), 3.80 (3 s), OCH_3 protons; 6.6 δ (1 s, aromatic proton)

Mass spectrum: 206 (90) [$\text{C}_{12}\text{H}_{14}\text{O}_3$];
m/e (rel. abund.)

Anal. Calc. for $\text{C}_{12}\text{H}_{14}\text{O}_3$: C, 69.88; H, 6.84

Found: C, 68.03; H, 6.77

4,7-Dimethoxy-5-methyl-2-indanone oxime

A solution of 4,7-dimethoxy-5-methyl-2-indanone (1.0 g) and hydroxylamine hydrochloride (2.0 g) in ethanol

(10 ml) and pyridine (5 ml) was heated at 80° for five hours. The solvent was evaporated and the residue suspended in water, then filtered. The solid (0.98 g) was crystallized from ethanol to yield the title compound, m.p. 164-166°C.

I.r. spectrum: 3250 cm^{-1} br (OH)

N.m.r. spectrum (DMSO- d_6): 2.23 (3 s, CH_3); 3.23-3.85 (10 m, OCH_3 and CH_2 protons); 6.71 (1 s, aromatic proton); 10.66 δ (1 s, OH)

Anal. Calc. for $\text{C}_{12}\text{H}_{15}\text{NO}_3$: C, 65.14; H, 6.83;

N, 6.33

Found: C, 64.69; H, 6.92;

N, 5.99

Reduction of 4,7-dimethoxy-5-methyl-2-indanone oxime

a) catalytic hydrogenation

A solution of the oxime of 4,7-dimethoxy-5-methyl-2-indanone (0.6 g) in ethanol (100 ml) was hydrogenated at room temperature and pressure in the presence of 10% palladium-charcoal (0.1 g). Less than the theoretical amount of hydrogen was absorbed after 48 hours. Starting material (0.4 g) was recovered.

The oxime (0.5 g) was hydrogenated in the presence of platinum oxide (0.05 g) for four days; less than the theoretical amount of hydrogen was absorbed. The catalyst was removed by filtration and the solvent evaporated,

leaving a semi-solid residue. Dissolution of this residue in chloroform and ether followed by saturation with hydrogen bromide gas caused the solution to turn dark brown. Evaporation of the solvent left a hygroscopic solid which liquified. Attempts to isolate a crystalline product failed.

b) with lithium aluminum hydride

A suspension of the oxime of 4,7-dimethoxy-5-methyl-2-indanone (0.5 g) in sodium dried ether (50 ml) was slowly added to a stirred suspension of lithium aluminum hydride (0.5 g) in the same solvent (100 ml). The mixture was then heated under reflux for 40 hours, cooled, and the excess lithium aluminum hydride decomposed with water. The thick suspension was filtered and the insoluble cake was washed thoroughly with ether (200 ml). The combined ether fractions were dried with magnesium sulfate, concentrated to 50 ml, then saturated with gaseous hydrogen chloride. This caused the precipitation of 0.08 g of solid which was collected by filtration. Evaporation of the filtrate left a small amount of dark-colored oil. Dissolution of this oil in acetone left an additional 0.04 g of solid. Recrystallization of the combined solids from ethanol-ether yielded a white crystalline product, m.p. 253-255°C.

I.r. spectrum: 1610, 2020, 2500-2680 cm^{-1} (N^+-H)

c) catalytic reduction in acetic acid and sulfuric acid

The oxime of 4,7-dimethoxy-5-methyl-2-indanone (0.5 g) in glacial acetic acid (50 ml) and sulfuric acid (0.5 g) was hydrogenated at room temperature and pressure in the presence of 10% palladium-charcoal (0.13 g) until the absorption of hydrogen ceased (three hours). After the catalyst had been removed by filtration, the clear filtrate was treated with sodium hydroxide (0.25 g) in water (2 ml). The acetic acid was evaporated under reduced pressure. The residue which remained was dissolved in water (50 ml), basified with 5% sodium hydroxide (3 ml), then extracted with chloroform. Saturation of the chloroform extract with hydrogen chloride gas followed by evaporation of the solvent left a white solid residue. This material was suspended in acetone, then filtered. The solid (0.22 g) was crystallized from ethanol and ether to yield a product melting at 253-255°C. A mixed melting point determination with the product isolated after lithium aluminum hydride reduction, described above, was undepressed.

d) catalytic reduction in ethanol and hydrochloric acid

A solution of the oxime of 4,7-dimethoxy-5-methyl-2-indanone (0.5 g) in ethanol (200 ml) and hydrochloric acid (5 ml) was hydrogenated at room temperature and pressure under platinum oxide (0.1 g). After the theoretical amount of hydrogen was absorbed, the catalyst was removed by filtration and the solvent evaporated. The residue which

remained was stirred with water, then filtered. The clear filtrate was evaporated under reduced pressure, leaving an oil which crystallized from ethanol-ether to give a product (0.185 g), m.p. 253-255°C. Mixed melting point determinations with the products described immediately above were undepressed. This material was 2-amino-4,7-dimethoxy-5-methylindane hydrochloride.

I.r. spectrum: 1610, 2220-2680 cm^{-1} (N-H^+)

N.m.r. spectrum (D_2O): 2.3 (3 s, CH_3); 2.9-3.6 (4 m, CH_2); 3.83 (3 s), 3.88 (3 s), OCH_3 protons; 4.1-4.6 (1 m, CH); 6.83 δ (1 s, aromatic proton)

Anal. Calc. for $\text{C}_{12}\text{H}_{18}\text{ClNO}_2$: C, 59.12; H, 7.45;
N, 5.75

Found: C, 58.70; H, 7.64;
N, 5.85

2-Amino-4,7-dimethoxy-5-methylindane hydrochloride

A solution of 2-amino-4,7-dimethoxy-6-methylindanol hydrochloride (0.5 g) in 10% hydrochloric acid (50 ml) was hydrogenated at room temperature and pressure in the presence of 10% palladium-charcoal (0.1 g). No hydrogen was absorbed after eight hours. The same material (0.4 g) in dioxane (20 ml) and concentrated hydrochloric acid (20 ml) was similarly hydrogenated in the presence of 10% palladium-charcoal (0.1 g). Hydrogen was slowly absorbed over 20 hours. The catalyst was removed by filtration and

the solvent was evaporated under reduced pressure. The solid residue was then suspended in acetone and filtered. This material (0.2 g) was, on the basis of i.r. spectral comparisons and mixed melting point determinations, identified as 2-amino-4,7-dimethoxy-5-methylindane hydrochloride.

The acetone filtrate was evaporated and the residue dissolved in water, then filtered. A small amount of 4,7-dimethoxy-5-methyl-2-indanone was recovered. The aqueous filtrate was basified with 5% sodium hydroxide, then extracted with chloroform. Saturation of this latter solution with hydrogen chloride gas, followed by evaporation of the solvent, left cis-2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride (0.2 g), m.p. 208°C.

The reaction described immediately above was repeated on the free base of 2-amino-4,7-dimethoxy-6-methyl-1-indanol (2.0 g) in dioxane (100 ml) and hydrochloric acid (100 ml) and palladium-charcoal (0.3 g). The reaction was continued for three days, with 0.1 g of catalyst being added each day. Following the procedure described above yielded 0.70 g of 2-amino-4,7-dimethoxy-5-methylindane hydrochloride and 0.78 g of cis-2-amino-4,7-dimethoxy-6-methyl-1-indanol.

I.r. spectrum: 1600, 2480-2700 (N-H^+);
3150 cm^{-1} br (OH)

Mass spectrum: 223 (75) [$\text{C}_{12}\text{H}_{17}\text{NO}_3$];
m/e (% rel. abund.)

Anal. Calc. for $C_{12}H_{18}ClNO_3$: C, 55.49; H, 6.98;
N, 5.39

Found: C, 55.26; H, 7.24;
N, 5.68

Hydrogenation of 2-amino-4,7-dimethoxy-6-methyl-1-indanone hydrochloride in the presence of palladium-charcoal and palladium chloride

A solution of 2-amino-4,7-dimethoxy-6-methyl-1-indanone hydrochloride (0.5 g) in ethanol (50 ml) was hydrogenated at 50 psi and room temperature for 15 hours (arbitrary) in the presence of palladium-charcoal (0.1 g) and palladium chloride (0.1 g). The catalyst was removed and the solvent evaporated. The residue was crystallized from ethanol and ether and yielded a compound (0.3 g), m.p. 202-207°C, whose i.r. spectrum was superimposable on the i.r. spectrum of cis-2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride.

Isomerization of trans-2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride with hydrochloric acid

A solution of the title compound (1.0 g) in concentrated hydrochloric acid was heated on a water bath (80°) for 30 minutes. The solvent was then removed under reduced pressure and room temperature. A white solid remained.

I.r. spectrum: 3150 (cis-OH); 3350 (trans-OH); absorption at 1750 cm^{-1} (C=O) was absent

When the above mixture was heated for three hours at

80° followed by removal of the solvent at 80° and at reduced pressure a white solid remained.

I.r. spectrum: 3150 (cis-OH); absorption at 3350 (trans-OH) was absent; a weak band at 1750 cm^{-1} (C=O) was present

Preparation of magnesium methyl carbonate (2 M)

Magnesium turnings (60.0 g) were added to anhydrous methanol (1000 ml) in a 2 litre flask equipped with a reflux condenser, stirrer and provision for passing carbon dioxide over the liquid, at a rate to maintain constant but controllable reflux. Upon completion of the reaction, the excess methanol was removed by evaporation under reduced pressure; sufficient methanol was left to maintain solution. Dimethylformamide was then added to give a total volume of 1.25 litres. Carbon dioxide was admitted to the stirred solution at a sufficient rate to maintain positive pressure. The magnesium methoxide was expected to dissolve completely; this occurred very slowly, and the solution acquired a 'jelly-like' consistency (probably magnesium hydroxide). The excess methanol was distilled until the head temperature reached 150°; the reaction was cooled to room temperature under carbon dioxide. The resultant preparation consisted of a solid suspended in a gel-like medium instead of the expected light yellow liquid. The reaction was repeated and similar results obtained.

Attempted preparation of 2-nitro-3-(2,5-dimethoxy-4-methylphenyl)propionic acid

Magnesium methyl carbonate (2 M, 100 ml) was placed in a 500 ml flask equipped with a stirrer, gas inlet, condenser and gas outlet. The reaction was heated while stirring at 60° under a carbon dioxide stream. 1-(2,5-Dimethoxy-4-methylphenyl)-2-nitroethane (12.5 g) was added and the carbon dioxide was replaced by a slow nitrogen stream. The reaction mixture was stirred at 60° for six hours, then poured into hydrochloric acid (75 ml), ice (100 g) and ether (20 ml). The ether was separated and the aqueous layer extracted four times with ether (25 ml portions). Removal of ether left 11.7 g of starting material. The reaction was repeated and similar results were obtained.

b) Reactions Related to the Preparation of 2-Amino-4,7-dimethoxy-6-methyl-1-substituted Indanes

Attempted synthesis of 2-amino-4,7-trimethoxy-6-methylindane

A solution of trans-2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride (0.5 g) in methanol (50 ml) and hydrochloric acid (5 ml) was heated under reflux for two hours. The residue which remained following evaporation of the solvent was negative to 2,4-DNP reagent. Crystallization of the residue from ethanol and ether yielded only starting material.

A solution of trans-2-amino-4,7-dimethoxy-6-methyl-1-

indanol hydrochloride (2.0 g) in methanol (150 ml) and hydrochloric acid (50 ml) was heated under reflux for 15 hours. The solvent was evaporated and the dried residue was suspended in acetone, then filtered. The solid (1.6 g) was crystallized from ethanol and ether to yield cis-2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride, m.p. 204-208°C. The acetone filtrate was evaporated and the gummy residue which remained was dissolved in water. The resulting suspension was filtered and 0.15 g of 4,7-dimethoxy-5-methyl-2-indanone was collected. The clear aqueous filtrate was evaporated, leaving a solid (0.38 g). Crystallization of this residue from ethanol yielded a product which melted between 200-202°. A mixed melting point with cis-2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride was depressed. This material was tentatively identified as 2,7,7-trimethyl-1,4-dimethoxyindano(1,2-d)-oxazolidine hydrochloride.

I.r. spectrum: 1020, 1170, 1240 (C-O); 1600, 2090, 2490-2710 cm^{-1} (N-H^+)

Mass spectrum: 263 (26) [$\text{C}_{15}\text{H}_{21}\text{NO}_3$];
m/e (% rel. abund.)

N.m.r. spectrum (D_2O): 2.28 (9 br s, CH_3 protons); 2.5-3.1 (1 m, CH); 3.22 (2 d, $J = 7$ cps, CH_2); 3.80 (6 br s, OCH_3 protons); 5.48 (1 d, $J = 6$ cps, CH); 6.95 δ (1 s, aromatic proton)

Anal. Calc. for $C_{15}H_{22}ClNO_3$: N, 4.67

Found: N, 4.68

2-Amino-4,7-dimethoxy-1-ethoxy-6-methylindane
hydrochloride

A solution of trans-2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride (1.0 g) in ethanol (50 ml) and hydrochloric acid (5 ml) was heated under reflux for 15 hours. The solvent was then evaporated and the oily residue was crystallized from ethanol and ether and successive crops were collected. Although this mixture was not completely separated into its components, cis-2-amino-4,7-dimethoxy-6-methylindane (0.28 g) and what was assumed to be the title compound (0.05 g) were recovered via fractional crystallization. The latter compound melted with decomposition at 278°C (ethanol-ether).

I.r. spectrum: 1050, 1070, 1235 (C-O);
1600 cm^{-1} ($\overset{+}{N}$ -H)

Mass spectrum: 251 (100) [$C_{14}H_{21}NO_3$];
m/e (% rel. abund.)

2-Amino-4,7-dimethoxy-6-methyl-1-propoxyindane
hydrochloride

A solution of trans-2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride (1.0 g) in propanol (50 ml) and hydrochloric acid (5 ml) was heated under reflux for 15 hours. The solvent was then evaporated and the residue

was crystallized from ethanol. It was very difficult to isolate pure compounds via fractional crystallization. Although the mixture was not completely separated, cis-2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride, m.p. 208°C, and a product melting between 248-256° (0.04 g) were collected. Crystallization of this latter material from ethanol and ether yielded what was assumed to be the title compound, m.p. 254-257°C.

I.r. spectrum: 1050, 1080, 1230 (C-O); 1600, 2000, 2560-2650 cm^{-1} ($\text{N}^+\text{-H}$)

Mass spectrum: 265 (40) [$\text{C}_{15}\text{H}_{23}\text{NO}_3$];
m/e (% rel. abund.)

2-Amino-1-chloro-4,7-dimethoxy-6-methylindane
hydrochloride

A solution of trans-2-amino-1-indanol hydrochloride (5.0 g) in hydrochloric acid (25 ml) and water (5 ml) was stirred at room temperature for 24 hours. Evaporation of the solvent at 30° under reduced pressure left a solid residue which was crystallized from ethanol and ether. Although the mixture was not completely separated, trans-2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride (1.4 g), cis-2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride (0.6 g), m.p. 204-206°C and an unknown compound (0.18 g), m.p. 154-157°C (ethanol) were collected. This latter material was tentatively identified as the title compound. Because of the difficulty experienced in separating the

desired product from the mixture, this reaction was not investigated further.

I.r. spectrum: 1630, 2050, 2550-2570 ($\overset{+}{N}$ -H);
3350, 3500 cm^{-1} (OH)

Mass spectrum: 243 (<5) [$\text{C}_{12}\text{H}_{16}^{37}\text{ClNO}_2$]; 241 (<5)
[$\text{C}_{12}\text{H}_{16}^{35}\text{ClNO}_2$]; m/e (% rel. abund.)

Anal. Calc. for $\text{C}_{12}\text{H}_{17}\text{ClNO}_2$: C, 51.81; H, 6.16;
N, 5.04

Found: C, 49.41; H, 6.72;
N, 3.61

When the above mixture of cis- and trans-4,7-dimethoxy-6-methyl-1-indanol hydrochloride was heated with hydrochloric acid at 75° for five hours followed by evaporation of the solvent, a residue consisting mainly of cis-4,7-dimethoxy-6-methyl-1-indanol was recovered. None of the 1-chloro derivative was isolated.

Attempted synthesis of 2-amino-1-chloro-4,7-dimethoxy-6-methylindane employing phosphorus pentachloride

A solution of trans-2-amino-4,7-dimethoxy-6-methyl-1-indanol (0.5 g) and phosphorus pentachloride (0.66 g) in dry dioxane was heated under reflux for ten minutes. Attempts to crystallize the dark residue which remained after evaporation of the solvent proved unsuccessful. Further investigations of this reaction were not undertaken.

c) Reactions Related to the Preparation of Some Derivatives of 2-Amino-4,7-dimethoxy-5-methylindane

Attempted synthesis of 2-bromo-4,7-dimethoxy-6-methyl-1-indanone

Bromine water was added dropwise to a solution of 4,7-dimethoxy-6-methyl-1-indanone (2.0 g) at a rate such that decolorization occurred between additions. A slight excess of bromine was added and the solution was then stirred for five hours. Removal of the solvent left a dark red-black oil. Attempts to isolate a pure material were unsuccessful. Further investigations of the oil were discontinued.

Bromine (1.5 ml) was added dropwise to a solution of 4,7-dimethoxy-6-methyl-1-indanone (4.1 g) in ether (200 ml) and methanol (200 ml). The mixture was stirred for two hours and then allowed to stand overnight. Evaporation of the solvent left a black oil which did not crystallize. Further investigation of the reaction was discontinued.

2-Dimethylamino-4,7-dimethoxy-5-methylindane hydrochloride

A solution of 2-amino-4,7-dimethoxy-5-methylindane hydrochloride (0.5 g) in water (30 ml) and 40% formaldehyde (0.6 g) was hydrogenated at room temperature and pressure over 10% palladium-charcoal (0.5 g) for 12 hours (arbitrary). The catalyst was removed by filtration and the filtrate was basified with ammonium hydroxide, then extracted with chloroform. The chloroform extract was

washed with water and saturated with hydrogen chloride gas. Removal of the solvent left a light yellow solid (0.2 g), m.p. 190-194°C. Crystallization did not occur readily and only a micro-crystalline material was isolated, m.p. 194-196°C (ethanol).

I.r. spectrum: 1600, 2400-2700 cm^{-1} ($\text{N}^+\text{-H}$)

Mass spectrum: 235 (57) [$\text{C}_{14}\text{H}_{21}\text{NO}_2$];

m/e (% rel. abund.)

Anal. Calc. for $\text{C}_{14}\text{H}_{22}\text{ClNO}_2$: C, 61.86; H, 8.16;

N, 5.15

Found: C, 61.87; H, 8.34;

N, 5.42

cis-2-Dimethylamino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride

A solution of cis-2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride (1.0 g) in water (30 ml) and 40% formaldehyde (1.5 g) was hydrogenated at room temperature and pressure in the presence of 10% palladium-charcoal (1.0 g) for 12 hours (arbitrary). The procedure described immediately above was then followed. The title compound was isolated (0.55 g), then crystallized from ethanol-ether, m.p. 234-236°C.

I.r. spectrum: 1610, 2500-2700 br ($\text{N}^+\text{-H}$);

3190 br cm^{-1} (OH)

Anal. Calc. for $C_{14}H_{22}ClNO_3$: C, 58.42; H, 7.71;

N, 4.87

Found: C, 58.67; H, 7.97;

N, 4.96

trans-2-Dimethylamino-4,7-dimethoxy-6-methyl-1-indanol
hydrochloride

The above procedure was repeated with trans-2-amino 4,7-dimethoxy-6-methyl-1-indanol hydrochloride. When the aqueous solution was basified with ammonium hydroxide, a solid (0.38 g) crystallized from the solution and was collected by filtration. When a solution of the dried solid in ether was saturated with gaseous hydrogen chloride a white solid precipitated from solution. It was collected by filtration, then crystallized from ethanol to yield the title compound, m.p. 245°C. A mixed melting point determination with the cis-isomer described immediately above was depressed.

I.r. spectrum: 1610, 2460-2560 ($N-H^+$);

3270 cm^{-1} br (OH)

Anal. Calc. for $C_{14}H_{22}ClNO_3$: C, 58.42; H, 7.71;
N, 4.87

Found: C, 58.72; H, 8.08;
N, 4.80

4,7-Dimethoxy-6-methyl-2-(dimethylamino)methyl-1-indanone hydrochloride

A solution of 4,7-dimethoxy-6-methyl-2-indanone (10.0 g), dimethylamine hydrochloride (4.05 g) and para-formaldehyde (3.0 g) in ethanol (150 ml) and hydrochloric acid (0.2 ml) was heated under reflux for three hours, then cooled. A solid crystallized from solution and was collected by filtration. The filtrate was concentrated by evaporation and successive crops were collected. The combined solids (7.2 g) were crystallized from ethanol and acetone to yield the title compound, m.p. 179-180°C.

I.r. spectrum: 1710 (C=O); 2450 br,
2550 br cm^{-1} ($\overset{+}{N}$ -H)

N.m.r. spectrum (DMSO- d_6): 2.22 (3 s, CH_3);
2.83 (6 s, NMe_2); 3.00-3.65 (5 m, CH and CH_2 protons);
3.75 (3 s), 3.84 (3 s), OCH_3 protons; 7.18 δ (1 s, aromatic
proton)

Anal. Calc. for $C_{15}H_{22}ClNO_3$: C, 60.09; H, 7.40
Found: C, 59.87; H, 7.67

4,7-Dimethoxy-6-methyl-2-(dimethylamino)methyl-1-indanol hydrochloride

A solution of 4,7-dimethoxy-6-methyl-2-(dimethylamino)methyl-1-indanone (3.0 g) in sodium dried ether (100 ml) was slowly added to a stirred suspension of lithium aluminum hydride (1.0 g) in the same solvent (100 ml). The mixture was heated under reflux for 12 hours, then cooled. The excess lithium aluminum hydride was decomposed with water and the suspension was filtered. The insoluble solid remaining was washed well with ether. The combined ether fractions (500 ml) were dried over magnesium sulfate, concentrated to 100 ml, and then saturated with gaseous hydrogen chloride. The solvent was removed, leaving a white solid (1.8 g) which slowly turned red. Attempts to crystallize the compound from ethanol, ethanol-ether, or ethanol-acetone failed.

A solution of 4,7-dimethoxy-6-methyl-2-(dimethylamino)methyl-1-indanone (2.0 g) in methanol (25 ml) was slowly added to a solution of sodium borohydride (1.0 g) in methanol (25 ml) and water (25 ml) over one hour. The solution was then stirred for one hour, after which time hydrochloric acid was added dropwise to the reaction mixture until effervescence ceased. The solution was basified with sodium bicarbonate, then evaporated. The residue was suspended in water and extracted with chloroform and the latter solution was collected, washed with water, then saturated with hydrogen chloride gas. Evaporation of the

solvent left a solid (1.1 g). Crystallization of the solid from ethanol yielded the title compound, m.p. 193-194°C.

I.r. spectrum: 2450, 2610 br (N-H^+);
3310 br cm^{-1} (OH)

Anal. Calc. for $\text{C}_{15}\text{H}_{24}\text{ClNO}_3$: C, 59.69; H, 8.01;
N, 4.64

Found: C, 59.69; H, 7.83;
N, 4.65

4,7-Dimethoxy-5-methyl-2-(dimethylamino)methylindane hydrochloride

A solution of 4,7-dimethoxy-6-methyl-2-(dimethylamino)methyl-1-indanol hydrochloride (1.0 g) in dioxane (20 ml) and hydrochloric acid (20 ml) was hydrogenated in the presence of palladium-charcoal (0.5 g) at 40 psi and room temperature for 12 hours (arbitrary). The catalyst and solvent were removed and the residue dried in a desiccator. The residue was then suspended in dry acetone and filtered. The insoluble solid material (0.67 g) was crystallized from ethanol and ether to yield the title compound, m.p. 204-205°C.

I.r. spectrum: 2560 br, 2600 br cm^{-1} (N-H^+)

Anal. Calc. for $\text{C}_{15}\text{H}_{24}\text{ClNO}_2$: C, 63.00; H, 8.46;
N, 4.90

Found: C, 62.50; H, 8.72;
N, 4.54

d) Reactions Related to the Synthesis of Miscellaneous 2-Aminoindanes

2,5-Dimethoxycinnamic acid

A solution of 2,5-dimethoxybenzaldehyde (50.0 g) and malonic acid (67.0 g) in pyridine (130 ml) and piperidine (5 ml) was heated under reflux for two hours, then poured into hydrochloric acid (150 ml) and ice-water (150 ml). The yellow precipitate (48.0 g) which formed was collected by filtration and washed with 5% hydrochloric acid, then distilled water. Crystallization from ethanol yielded the title compound, yellow needles, m.p. 145-146°C. Reported m.p. 147°C⁽²¹⁵⁾.

I.r. spectrum: 1690 (C=O); 2500-2700 cm^{-1} (OH)

Anal. Calc. for $\text{C}_{11}\text{H}_{12}\text{O}_4$: C, 63.45; H, 5.81

Found: C, 62.82; H, 5.64

3-(2,5-Dimethoxyphenyl)propionic acid

A solution of 2,5-dimethoxycinnamic acid (20.0 g) in ethanol (200 ml) with 10% palladium-charcoal (1.0 g) suspended by stirring, was hydrogenated at room temperature and pressure. When the uptake of hydrogen ceased, the catalyst was removed by filtration and the solvent was evaporated, leaving a quantitative yield of the title compound, m.p. 62-65°C (ethanol). Reported m.p. 65-66°C⁽¹³²⁾.

I.r. spectrum: 1720 (C=O); 2550-2700 cm^{-1} (OH)

Anal. Calc. for $\text{C}_{11}\text{H}_{14}\text{O}_4$: C, 62.84; H, 6.71

Found: C, 62.61; H, 6.71

3-(2,5-Dimethoxy-4-nitrophenyl)propionic acid

To a solution of 3-(2,5-dimethoxyphenyl)propionic acid (7.0 g) and sodium nitrite (0.05 g) in glacial acetic acid (35 ml) was added dropwise nitric acid (6.0 ml) in water (30 ml). The resulting red solution was placed in an ice bath and stirred for one hour. The bulky yellow precipitate that formed was collected by filtration and thoroughly washed with water. The filtrate was diluted with water (150 ml), then extracted with chloroform. Removal of this solvent left a yellow solid, melting at the same temperature as the precipitate. The combined solids (6.2 g) were crystallized from ethanol to yield the title compound, m.p. 120.5-123°C.

I.r. spectrum: 1340, 1570 (NO_2); 1710 (C=O);
2500-2700 cm^{-1} (OH)

N.m.r. spectrum (CDCl_3): 2.5-3.15 (4 m, CH_2);
3.83 (1 s), 3.88 (1 s), OCH_3 protons; 6.97 (1 s), 7.41 (1 s),
aromatic protons; 9.71 (1 br s, exchanges with D_2O , OH)

Anal. Calc. for $\text{C}_{11}\text{H}_{13}\text{NO}_4$: C, 51.97; H, 4.76;
N, 5.51

Found: C, 51.89; H, 4.99;
N, 5.48

Attempted cyclization of 3-(2,5-dimethoxy-4-nitro-phenyl)propionic acid with:

a) polyphosphoric acid

3-(2,5-dimethoxy-4-nitrophenyl)propionic acid (2.0 g)

was placed in polyphosphoric acid (20.0 g) at 60° for 30 minutes, then added to ice-water (100 ml). The resulting precipitate was collected by filtration. This product was completely soluble in a 5% sodium bicarbonate solution. Acidification of this basic solution with hydrochloric acid caused the precipitation of starting material (1.52 g).

Heating an identical mixture in an oil bath to 100° caused no change in color from that observed in the reaction described immediately above. When the temperature was raised to 120°, the reaction mixture started to turn dark brown. It was then poured into ice-water and a black tarry material settled to the bottom of the container. Extraction of this mixture with chloroform, followed by evaporation of the solvent left a negligible residue. The chloroform insoluble tarry material was negative to 2,4-DNP reagent, therefore it was not investigated further.

b) sulfuric acid

3-(2,5-Dimethoxy-4-nitrophenyl)propionic acid (1.0 g) was stirred in sulfuric acid (10 ml) at room temperature for two hours, then poured into ice water. The precipitate was collected and dried. Mixed melting point determinations showed it to be starting material.

The reaction was repeated at 60° for two hours, then added to ice water. A dark brown solution without any precipitate formed. Extraction of the solution with chloroform failed to yield any product.

Starting material was obtained when an identical mixture was stirred in sulfuric acid at room temperature for 24 hours.

3-(4-Amino-2,5-dimethoxyphenyl)propionic acid

A solution of 3-(2,5-dimethoxy-4-nitrophenyl)propionic acid (12.0 g) in ethanol (200 ml) was hydrogenated at room temperature and pressure in the presence of 10% palladium-charcoal (1.0 g). A precipitate remained in the reaction flask after the theoretical volume of hydrogen was absorbed. The mixture was heated until dissolution was attained, then filtered to remove the catalyst. Evaporation of the solvent gave a quantitative yield of the title compound, m.p. 134-135°C (ethanol).

I.r. spectrum: 1700 br (C=O); 2500-2700 (OH); 3200, 3400 cm^{-1} (NH_2)

Anal. Calc. for $\text{C}_{11}\text{H}_{15}\text{NO}_4$: C, 58.91; H, 6.69;
N, 6.25

Found: C, 58.84; H, 6.67;
N, 6.34

3-(4-Acetamido-2,5-dimethoxyphenyl)propionic acid

A solution of 3-(4-amino-2,5-dimethoxyphenyl)propionic acid hydrochloride (10.0 g) in water (100 ml) and acetic anhydride (45.0 ml) was shaken vigorously until the evolution of heat ceased. Sodium acetate (50.0 g)

in water (50 ml) was added to the reaction mixture and on cooling the title compound precipitated from solution and was collected by filtration (10.2 g). Crystallization from ethanol yielded this product as a white solid, m.p. 186-188°C.

I.r. spectrum: 1630 (amide C=O); 1730 (acid C=O); 2500-2700 (OH); 3260 cm^{-1} br (NH)

Anal. Calc. for $\text{C}_{13}\text{H}_{17}\text{NO}_5$: C, 58.41; H, 6.41;
N, 5.24

Found: C, 58.55; H, 6.34;
N, 5.25

Cyclization of 3-(4-acetamido-2,5-dimethoxyphenyl)propionic acid with:

a) polyphosphoric acid

3-(4-Acetamido-2,5-dimethoxyphenyl)propionic acid (10.0 g) in polyphosphoric acid (100 g) was heated for 30 minutes at 85°; only a slight color change (light green) was observed. Addition of this reaction mixture to water resulted in the formation of a white precipitate. Mixed melting point determinations showed it to be identical with starting material (8.9 g).

The same material in polyphosphoric acid was heated on a glycerine bath until the solution became yellow (100-120°), then added to water. No precipitate formed. When a portion of the solution was basified no precipitate formed. The solution was, however, positive to 2,4-DNP

reagent. Extraction of the solution with chloroform followed by its evaporation left 6-acetamido-4,7-dimethoxy-1-indanone (0.12 g). It was crystallized from ethanol, m.p. 175.5-177.5°C.

I.r. spectrum: 1665 (amide C=O); 1710 (ketone C=O); 3310 cm^{-1} (NH)

Anal. Calc. for $\text{C}_{13}\text{H}_{15}\text{NO}_4$: C, 62.64; H, 6.07;
N, 5.62

Found: C, 62.65; H, 6.46;
N, 5.50

3-(4-Acetamido-2,5-dimethoxyphenyl)propionic acid (3.0 g) in polyphosphoric acid (30 g) was heated at 120° for ten minutes, then poured into water. Extraction of the resulting solution with chloroform yielded the indanone (0.86 g).

Heating an identical mixture for ten minutes at 130°, then following the above procedure, yielded crude material (1.2 g) from which was isolated 6-acetamido-4,7-dimethoxy-1-indanone (0.7 g).

Treating 3-(4-acetamido-2,5-dimethoxyphenyl)propionic acid (6.0 g) in polyphosphoric acid (60 g) at 120° for 40 minutes as described above yielded the crude product (2.6 g) from which was isolated pure indanone (1.4 g).

b) sulfuric acid

A solution of 3-(4-acetamido-2,5-dimethoxyphenyl)pro-

pionic acid (1.0 g) in sulfuric acid (10 ml) was stirred at room temperature for 24 hours, then added to ice water. Extraction of the resulting suspension with chloroform yielded starting material (0.8 g). No indanone (2,4-DNP reagent) was detected.

Heating an identical solution at 70° for 12 hours, followed by its addition to ice-water gave a clear solution. Attempts to isolate a product by chloroform extraction was unsuccessful. This reaction was not investigated further.

6-Amino-4,7-dimethoxy-1-indanone hydrochloride

A suspension of 6-acetamido-4,7-dimethoxy-1-indanone (1.0 g) in 6N hydrochloric acid (50 ml) was heated at reflux temperature for three hours, then cooled. The solution was then extracted with chloroform. The aqueous portion was separated and evaporated to dryness, leaving the title compound (0.63 g). Crystallization of this material proved extremely difficult and the analysis was performed on an amorphous form (m.p. 203°C).

I.r. spectrum: 1610, 2600 (N-H^+); 1715 cm^{-1} (C=O)

Anal. Calc. for $\text{C}_{11}\text{H}_{14}\text{ClNO}_3$: C, 54.21; H, 5.79;
N, 5.75

Found: C, 53.93; H, 5.95;
N, 5.60

Preparation of 4,7-dimethoxy-1-indanone by cyclization of 3-(2,5-dimethoxyphenyl)propionic acid with:

a) polyphosphoric acid

3-(2,5-Dimethoxyphenyl)propionic acid was treated with polyphosphoric acid as described on page 241. When the mixture was heated to 50°, it turned a yellow color. Further heating caused the reaction mixture to turn dark red-black. After heating the reaction mixture for different lengths of time (see below), it was poured into ice-water. In each instance a red oil separated from the solution. The oil was then extracted with chloroform and evaporated to yield another red oil which gave a positive test with 2,4-DNP reagent. In an attempt to isolate the ketone from the crude reaction mixture, the oil was dissolved in chloroform and extracted with a 5% sodium bicarbonate solution. However, a very stable emulsion formed. Even after standing for two weeks it had not completely cracked. Addition of brine or cooling the emulsion did not hasten its separation.

When a solution of the crude reaction product in chloroform was similarly extracted with a 5% sodium bicarbonate solution, a less stable emulsion resulted. An even less stable emulsion occurred after a solution of the crude reaction product in ether was extracted with a 5% sodium bicarbonate solution. It cracked within a week.

The cyclization reaction was attempted employing the following conditions:

Propionic acid	Temperature	Time	Crude Indanone Recovered
1.0 g	60°	5 min	negligible
3.0 g	80°	10 min	1.5 g
8.0 g	80°	30 min	3.0 g
10.0 g	80°	1 hr	4.2 g
25.0 g	80°	2.5 hr	13.0 g
10.0 g	100°	15 min	6.0 g
25.0 g	100°	15 min	12.0 g

The crude indanone was recovered by evaporating the organic solvent, then crystallizing the residue from ethanol, m.p. 124-125°C. Reported m.p. 124-125°C⁽¹³²⁾.

I.r. spectrum: 1700 cm^{-1} (C=O)

Anal. Calc. for $\text{C}_{11}\text{H}_{12}\text{O}_3$: C, 68.73; H, 6.30

Found: C, 68.51; H, 6.19

b) phosphorus pentoxide

Phosphorus pentoxide (40 g) was added to a solution of 3-(2,5-dimethoxyphenyl)propionic acid (10.0 g) in dried benzene (250 ml). The mixture was stirred and heated on a steam bath for 2.5 hours. The phosphorus pentoxide was then decomposed with water and the organic layer collected. The aqueous layer was extracted with ether (300 ml) and combined with the other organic fraction. After washing the organic fraction with a 5% sodium carbonate solution, the solvent was evaporated, leaving 3.2 g of 4,7-dimethoxy-1-indanone.

The reaction was repeated with 35.0 g of 3-(2,5-dimethoxyphenyl)propionic acid, except the reaction time was extended to five hours. Employing the reaction procedure described immediately above yielded 8.7 g of 4,7-dimethoxy-1-indanone.

4,7-Dimethoxy-6-nitro-1-indanone

A solution of nitric acid (10 ml) in water (30 ml) was added dropwise to a stirred solution of 4,7-dimethoxy-1-indanone (10.0 g) and sodium nitrite (0.2 g) in glacial acetic acid (50 ml). The solution was stirred for one hour, then diluted with ice-water (200 ml). The resulting yellow suspension was extracted with chloroform. Evaporation of the chloroform left a yellow solid (6.8 g) which was crystallized from ethanol to yield the title compound, m.p. 162-163°C.

I.r. spectrum: 1340, 1520 (NO_2); 1710 cm^{-1} (C=O)

Anal. Calc. for $\text{C}_{11}\text{H}_{11}\text{NO}_5$: C, 55.69; H, 4.67

Found: C, 56.04; H, 4.67

6-Amino-4,7-dimethoxy-1-indanone hydrochloride

4,7-Dimethoxy-6-nitro-1-indanone (2.0 g) was suspended in ethanol (50 ml) and hydrogenated at room temperature and pressure in the presence of palladium-charcoal (0.1 g). When the theoretical quantity of hydrogen was absorbed, the catalyst was removed by filtration and

the solvent was evaporated, leaving a semi-solid residue. Attempts to crystallize the semi-solid failed. This crude material was extracted with 5% hydrochloric acid, then evaporated to yield a solid product (0.7 g). Crystallization from ethanol yielded a product, m.p. 200-203°C, which, by mixed melting point determinations, was identified as the title compound.

4,7-Dimethoxy-2-nitroso-1-indanone

Ethyl nitrite gas was slowly bubbled into a solution of 4,7-dimethoxy-1-indanone (5.0 g) in ethanol (100 ml) and hydrochloric acid (10 ml). A solid material crystallized from the solution after approximately 20 minutes. After this material was removed by filtration, the filtrate was further treated with ethyl nitrite and this procedure was repeated until no more solid formed (approximately two hours). The combined solids (3.9 g) were dissolved in 10% sodium hydroxide, filtered, and then acidified with hydrochloric acid to yield the title compound, m.p. 233-234.5°C.

I.r. spectrum: 1650 (C=N); 1732 (C=O);
3300 cm^{-1} br (OH)

Anal. Calc. for $\text{C}_{11}\text{H}_{11}\text{NO}_4$: C, 59.72; H, 5.01

Found: C, 59.50; H, 4.97

2-Amino-4,7-dimethoxy-1-indanone hydrochloride

A suspension of 4,7-dimethoxy-2-isonitroso-1-indanone (5.0 g) in ethanol (200 ml) and hydrochloric acid (5 ml) was hydrogenated at room temperature and pressure in the presence of palladium-charcoal until the theoretical amount of hydrogen was absorbed. The catalyst was then removed by filtration and the solvent evaporated, leaving a white solid (4.5 g), which when crystallized from ethanol, yielded the title compound, m.p. 260-262°C.

I.r. spectrum: 1590, 1980, 2610-2700 (N-H^+);
1710 cm^{-1} (C=O)

Anal. Calc. for $\text{C}_{11}\text{H}_{14}\text{ClNO}_3$: C, 54.21; H, 5.79;
N, 5.75

Found: C, 53.98; H, 5.98;
N, 6.00

2-Amino-4,7-dimethoxy-1-indanol hydrochloride

A solution of 4,7-dimethoxy-2-isonitroso-1-indanone (3.0 g) in ethanol (100 ml) and 5% sodium hydroxide solution (10 ml) was hydrogenated at room temperature and pressure in the presence of palladium-charcoal (0.2 g) until the theoretical amount of hydrogen was absorbed. The residue which remained after removal of the catalyst and solvent was suspended in water and extracted with chloroform. The chloroform layer was washed with water, saturated with hydrogen chloride gas, and then evaporated, leaving a

solid (1.98 g). Crystallization of this material from ethanol yielded the title compound, m.p. 182-184°C.

I.r. spectrum: 1600, 2080, 2580-2660 (N-H^+);
3350 cm^{-1} br (OH)

Anal. Calc. for $\text{C}_{11}\text{H}_{16}\text{ClNO}_3$: C, 53.77; H, 6.56;
N, 5.70

Found: C, 53.68; H, 7.11;
N, 6.02

2-Amino-4,7-dimethoxyindane hydrochloride

A solution of 2-amino-4,7-dimethoxy-1-indanol (1.0 g) in dioxane (20 ml) and hydrochloric acid (20 ml) was hydrogenated at room temperature and pressure under palladium-charcoal (0.2 g) for 15 hours (arbitrary). The catalyst and solvent were removed and the solid residue was dried, suspended in acetone, and then filtered. This solid material (0.91 g) was crystallized from ethanol and ether to yield the title compound, m.p. 245-247°C.

I.r. spectrum: 1615, 2030, 2380-2700 cm^{-1} (N-H^+)

Mass spectrum: 193 (86) [$\text{C}_{11}\text{H}_{15}\text{NO}_2$];
m/e (% rel. abund.)

N.m.r. spectrum (D_2O): 3.18 (4 t, $J = 6$ cps, CH_2);
3.88 (6 s, OCH_3); 3.94-4.40 (1 m, CH);, 6.91 δ (2 s,
aromatic protons)

Anal. Calc. for $C_{11}H_{16}ClNO_2$: C, 57.51; H, 7.02;
N, 6.10

Found: C, 57.43; H, 7.16;
N, 6.23

2-Acetamido-4,7-dimethoxyindane

A solution of 2-amino-4,7-dimethoxyindane hydrochloride (1.0 g) in water (15 ml) and acetic anhydride (10 ml) was gently heated to initiate the reaction, then shaken vigorously until the evolution of heat ceased. A solution of sodium acetate (5.0 g) in water (10 ml) was added and the reaction mixture was cooled. When no solid precipitated from this solution, the solvent was evaporated and the residue suspended in 5% hydrochloric acid, then filtered. The insoluble portion (0.52 g) was collected, then crystallized from ethanol to yield the title compound, m.p. 143-146°C.

I.r. spectrum: 1640 (C=O); 3260 cm^{-1} (NH)

Mass spectrum: 235 (15) [$C_{13}H_{17}NO_3$];

m/e (% rel. abund.)

Anal. Calc. for $C_{13}H_{17}NO_3$: N, 5.98

Found: N, 5.42

Attempted synthesis of 2-acetamido-4,7-dimethoxy-5-nitroindane

A solution of nitric acid (1 ml) in water (4 ml) was added dropwise to a stirred solution of 2-acetamido-4,7-

dimethoxyindane (1.0 g) and sodium nitrite (0.01 g) in acetic acid (10 ml). The solution was stirred for one hour, then diluted with ice water (100 ml). This resulted in the precipitation of a red gummy product. The mixture was extracted with chloroform, then evaporated, leaving another red tarry compound. Attempts to crystallize this material from a variety of solvents including ethanol, ethanol and water, and acetone and water, were unsuccessful. The crude material was then suspended in a 20% sodium hydroxide solution (25 ml) and heated under reflux for two hours. The cooled solution was then extracted with chloroform. Evaporation of the chloroform left a red tarry material which was insoluble in 5% hydrochloric acid. This reaction was not investigated further.

2-Amino-5-bromo-4,7-dimethoxyindane hydrochloride

A solution of bromine in chloroform (5%) was added dropwise to a solution of 2-amino-4,7-dimethoxyindane (0.5 g) in chloroform (40 ml) and ethanol (10 ml). After the addition of approximately 5 drops of bromine solution, the reaction mixture was colored red; even after stirring eight hours the red color had not disappeared. The solvent was then evaporated and starting material was recovered.

A similar result was obtained after bromine and chloroform were added to 2-amino-4,7-dimethoxyindane (0.5 g) in ethanol (20 ml).

When a solution of bromine water was added dropwise to a stirred solution of 2-amino-4,7-dimethoxyindane hydrochloride (0.5 g) in ethanol (20 ml), the red color of bromine disappeared after the addition of each drop. A slight excess of bromine water was added to the solution, then it was stirred for two hours. The solution was basified with 5% sodium bicarbonate solution and evaporated. The residue was suspended in water and extracted with chloroform. Evaporation of this latter solvent left a red-brown oil. A solution of this oil in chloroform was then extracted with 5% hydrochloric acid. Evaporation of this latter solvent left a solid residue (0.22 g). Crystallization of this material from ethanol yielded a monobrominated derivative of 2-amino-4,7-dimethoxyindane, m.p. 235-237°C. This material was assumed to be 2-amino-5-bromo-4,7-dimethoxyindane hydrochloride.

I.r. spectrum: 1600, 2050, 2590-2690 cm^{-1} (N-H^+)

Mass spectrum: 273 (30) [$\text{C}_{11}\text{H}_{14}^{81}\text{BrNO}_2$]; 271 (30) [$\text{C}_{11}\text{H}_{14}^{79}\text{BrNO}_2$]; m/e (% rel. abund.)

Bromine water was added dropwise to a solution of 2-amino-4,7-dimethoxyindane hydrochloride (0.4 g) in water (20 ml) until a slight red color persisted. The solution was then stirred for two hours, after which time it was basified with 5% sodium hydroxide. The red solution was then extracted with ether (30 ml). The latter solvent was collected, washed with water, saturated with hydrogen

chloride gas, and then evaporated, leaving a white solid (0.14 g). Crystallization of this material yielded a compound identical with the brominated derivative just described, m.p. 236-237°C.

3-(4-Bromo-2,5-dimethoxyphenyl)propionic acid

A solution of bromine in chloroform was added to a solution of 3-(2,5-dimethoxyphenyl)propionic acid (4.0 g) in chloroform (100 ml) as described on page 279. Starting material, however, was recovered from the reaction.

When bromine water was added to a solution of 3-(2,5-dimethoxyphenyl)propionic acid (9.0 g) in ethanol (100 ml), the red color of bromine disappeared. A slight excess of bromine water was added, then the solution was stirred for four hours. Evaporation of the solvent left an oil which was dissolved in chloroform and extracted with 5% sodium hydroxide solution. Acidification of the aqueous extract with hydrochloric acid gave a solid (5.4 g) which, when crystallized from ethanol, yielded 3-(4-bromo-2,5-dimethoxyphenyl)propionic acid, m.p. 136-137°C.

I.r. spectrum: 1700 (C=O); 2500-2700 cm^{-1} (OH)

N.m.r. spectrum (CDCl_3): 2.52-3.12 (4 m, CH_2 protons); 3.76 (3 s), 3.81 (3 s), OCH_3 protons; 6.80 (1 s), 7.03 (1 s), aromatic protons; 11.36 δ (1 br s, exchanges with D_2O , OH)

Anal. Calc. for $C_{11}H_{13}BrO_4$: C, 45.69; H, 4.53

Found: C, 45.63; H, 4.53

Evaporation of the chloroform solution left a red oil [i.r. 1740 cm^{-1} (ester)] which, when heated in 10% sodium hydroxide solution under reflux for one hour and then acidified, yielded 3-(4-bromo-2,5-dimethoxyphenyl)propionic acid (3.4 g).

When bromine water was added dropwise to a stirred solution of 3-(2,5-dimethoxyphenyl)propionic acid (25 g) in dioxane (100 ml) and water (25 ml), 3-(4-bromo-2,5-dimethoxyphenyl)propionic acid crystallized from solution. The solid was collected by filtration and more bromine water was added to the reaction mixture, causing the crystallization of additional 3-(4-bromo-2,5-dimethoxyphenyl)propionic acid. When a slight excess of bromine had been added, the solution was diluted with water to precipitate more product. The combined solids (22.2 g) crystallized from ethanol and water and yielded the title compound.

6-Bromo-4,7-dimethoxy-1-indanone

The cyclization was undertaken as described on page 241. When 3-(4-bromo-2,5-dimethoxyphenyl)propionic acid (10.0 g) was heated in polyphosphoric acid (100 g) at 100° for one hour, a solid material (2.6 g) was collected from the chloroform extract. Crystallization of this material

from ethanol yielded the title compound, m.p. 109°C.

I.r. spectrum: 1700 cm^{-1} (C=O)

Anal. Calc. for $\text{C}_{11}\text{H}_{11}\text{BrO}_3$: C, 48.73; H, 4.09

Found: C, 48.56; H, 4.08

6-Bromo-4,7-dimethoxy-2-isonitroso-1-indanone

Freshly generated ethyl nitrite gas was slowly bubbled into a solution of 6-bromo-4,7-dimethoxy-1-indanone (3.0 g) in ethanol (60 ml) and hydrochloric acid (5 ml) using the method described on page 275. A total of 1.2 g of solid was recovered. It melted with decomposition between 245-250°C. Although it was not purified, it was assumed to be the title compound.

I.r. spectrum: 1650 (C=N) ; 1730 (C=O) ;
 3300 cm^{-1} br (OH)

Catalytic hydrogenation of 6-bromo-4,7-dimethoxy-2-isonitroso-1-indanone in:

a) ethanol and hydrochloric acid

A solution of 6-bromo-4,7-dimethoxy-2-isonitroso-1-indanone (0.6 g) in ethanol (50 ml) and hydrochloric acid (3 ml) was hydrogenated at room temperature and pressure in the presence of palladium-charcoal (0.2 g) for 12 hours (arbitrary). Removal of the catalyst and solvent left a compound which had an i.r. spectrum superimposable on the i.r. spectrum of 2-amino-4,7-dimethoxy-1-indanone hydrochloride. A mixture of these two materials did not show

a depression in the melting point.

b) ethanol and sodium hydroxide

A solution of 6-bromo-4,7-dimethoxy-2-isonitroso-1-indanone (1.0 g) in ethanol (100 ml) and 5% sodium hydroxide (5 ml) was hydrogenated at room temperature and pressure in the presence of palladium-charcoal (0.1 g) for 12 hours (arbitrary). The catalyst and solvent were removed and the residue was suspended in water and extracted with chloroform. After the chloroform layer was collected, it was washed well with water, saturated with gaseous hydrogen chloride, and then evaporated. The solid residue (0.64 g) was crystallized from ethanol, m.p. 180-182°C. The i.r. spectrum of this compound was superimposable on that of 2-amino-4,7-dimethoxy-1-indanol hydrochloride. A mixture of these two materials failed to show a depression in their melting point.

Hydrogenation of 3-(4-bromo-2,5-dimethoxyphenyl)propionic acid

A solution of 3-(4-bromo-2,5-dimethoxyphenyl)propionic acid (1.0 g) in ethanol (50 ml) was hydrogenated at 20 psi and room temperature in the presence of palladium-charcoal (0.1 g) for 12 hours. The catalyst and solvent were removed and an oil, which was insoluble in a 5% sodium hydroxide solution, remained. The oil was suspended in 10% sodium hydroxide solution (20 ml), then heated under

reflux for one hour. The cooled solution was then acidified with hydrochloric acid and the resultant precipitate collected. The i.r. spectrum of this material was superimposable on the i.r. spectrum of 3-(2,5-dimethoxyphenyl)propionic acid. A mixture of these two materials did not show any depression of their melting point.

4-Methoxycinnamic acid

A solution of *p*-methoxybenzaldehyde (65.0 g) and malonic acid (87.0 g) in pyridine (150 ml) and piperidine (7 ml) was heated under reflux for two hours, then poured into ice and hydrochloric acid (300 ml). The resulting precipitate was collected by filtration (63.0 g) and crystallized from ethanol to yield the title compound, m.p. 170-173°C. Reported m.p. 171.6-173°C⁽²⁰¹⁾.

I.r. spectrum: 1690 (C=O); 2450-2700 cm⁻¹ (OH)

3-(4-Methoxyphenyl)propionic acid

A suspension of 4-methoxycinnamic acid (50.0 g) in ethanol (300 ml) was hydrogenated at room temperature and pressure in the presence of palladium-charcoal (2.0 g) until the theoretical amount of hydrogen was absorbed. The catalyst and solvent were removed and the solid remaining was crystallized from ethanol to yield the title compound (50.0 g), m.p. 100-102°C. Reported m.p. 103-105°C⁽²⁰¹⁾.

I.r. spectrum: 1700 cm⁻¹ (C=O)

Preparation of 6-methoxy-1-indanone by cyclization of 3-(4-methoxyphenyl)propionic acid with:

a) polyphosphoric acid

After 3-(4-methoxyphenyl)propionic acid (15.0 g) in polyphosphoric acid (150.0 g) was heated at 80° for one hour, the reaction mixture was added to water. The resulting suspension was filtered, then washed with 5% sodium bicarbonate. The remaining solid, which turned to an oil on standing, was virtually negative to 2,4-DNP reagent. Attempts to crystallize this material were unsuccessful. Similar results were obtained when the reaction was carried out at higher temperatures and longer reaction times.

b) Friedel-Craft reaction conditions

3-(4-Methoxyphenyl)propionic acid (12 g) and phosphorus pentachloride (14.4 g) were mixed with shaking in a 500 ml round bottom flask. The mixture melted and hydrogen chloride gas evolved. After the flask was evacuated at 80°, the residue was dissolved in benzene (300 ml), then cooled. Aluminum chloride (9.6 g) was added to the mixture over 15 minutes, then it was stirred at room temperature for four hours. The dark red complex which formed was decomposed with ice and hydrochloric acid. The resulting suspension was extracted with ether. This extract was then washed with 2% potassium hydroxide and evaporated to give 6-methoxy-1-indanone (3.2 g), m.p. 108°C

(ethanol). Reported m.p. 108-109°C⁽²⁰¹⁾.

I.r. spectrum: 1695 cm⁻¹ (C=O)

2-Isonitroso-6-methoxy-1-indanone

Ethyl nitrite was slowly bubbled into a solution of 6-methoxy-2-indanone (12.0 g) in ethanol (300 ml) and hydrochloric acid (20 ml) as described on page 275. The combined solids which precipitated from solution (6.8 g) were dissolved in 10% aqueous sodium hydroxide. After filtering, the solution was acidified with hydrochloric acid to yield a precipitate of the title compound, m.p. 223-225°C. Reported m.p. 221°C⁽²¹⁶⁾.

Anal. Calc. for C₁₀H₉NO₃: C, 62.82; H, 4.74;
N, 7.33

Found: C, 62.86; H, 4.99;
N, 7.32

2-Amino-6-methoxy-1-indanol hydrochloride

A suspension of 2-isonitroso-6-methoxy-1-indanone (6.0 g) in ethanol (250 ml) and 10% sodium hydroxide solution (10 ml) was hydrogenated at room temperature and pressure in the presence of palladium-charcoal (0.6 g) for 12 hours (arbitrary). The catalyst and solvent were then removed, leaving a dark oil. This oil was suspended in water and extracted with chloroform. The latter extract was washed with water, saturated with gaseous hydrogen

chloride, and then evaporated. The residue was suspended in acetone and the insoluble material remaining (2.98 g), when crystallized from ethanol, yielded the title compound, m.p. 220-234°C. Reported m.p. 217-222°C and 210-232°C (119,124).

Anal. Calc. for $C_{10}H_{14}ClNO_2$: C, 55.68; H, 6.54;
N, 6.50

Found: C, 55.77; H, 6.60;
N, 6.78

2-Amino-5-methoxyindane hydrochloride

A solution of 2-amino-6-methoxy-1-indanol hydrochloride (0.1 g) in hydrochloric acid (50 ml) was hydrogenated at 40 psi and room temperature in the presence of palladium-charcoal (0.1 g) for two hours. An additional 0.2 g of palladium-charcoal was added to the mixture and hydrogenation was continued under the above conditions for six hours. After this time the catalyst and solvent were removed, leaving a solid residue (0.71 g). Crystallization of this material from ethanol yielded the title compound, m.p. 240-242°C. Reported m.p. 231-234°C⁽¹¹⁸⁾.

I.r. spectrum: 1605, 2020, 2500-2680 cm^{-1} ($\overset{+}{N}-H$)

N.m.r. spectrum (DMSO- d_6): 2.68-3.3 (4 m, CH_2); 3.54-4.15 (3 m, CH and OCH_3 protons); 6.54-7.32 (3 m, aromatic protons); 8.99 δ (3 br s, exchanges with D_2O , $\overset{+}{NH}_3$)

Anal. Calc. for $C_{10}H_{14}ClNO$: C, 60.15; H, 7.07;
N, 7.01

Found: C, 60.15; H, 7.26;
N, 6.69

e) Reactions Related to the Synthesis of 1-Aminoindanes
4,7-Dimethoxy-6-methyl-1-indanone oxime

A solution of 4,7-dimethoxy-6-methyl-1-indanone (7.0 g), hydroxylamine hydrochloride (7.0 g) in ethanol (100 ml), and pyridine (8 ml) was heated on a water bath at 80° with occasional shaking. After ten minutes a precipitate formed. The solution was heated for an additional 15 minutes, cooled, and then filtered. The solid (5.7 g) was washed well with 5% hydrochloric acid, then crystallized from methanol to yield the title compound, m.p. 228-231°C.

I.r. spectrum: 3250 cm^{-1} br (OH)

Anal. Calc. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83
Found: C, 65.10; H, 6.79

Preparation of 1-amino-4,7-dimethoxy-6-methylindane hydrobromide by reduction of 4,7-dimethoxy-6-methyl-1-indanone oxime with:

a) lithium aluminum hydride

A suspension of finely powdered oxime of 4,7-dimethoxy-6-methyl-1-indanone (4.5 g) in sodium dried ether (200 ml) was slowly added to a stirred suspension of

lithium aluminum hydride (1.0 g) in the same solvent (100 ml). The mixture was then heated under reflux for 30 hr cooled, and the excess lithium aluminum hydride decomposed with water. The suspension was filtered and the insoluble material washed well with ether. The combined ether fractions were dried over magnesium sulfate, then saturated with hydrogen bromide gas. The precipitate (4.8 g) which formed was collected by filtration and crystallized from ethanol to yield 1-amino-4,7-dimethoxy-6-methylindane hydrobromide, m.p. 213.5-214.5°C.

I.r. spectrum: 1590, 2000, 2580-2680 cm^{-1} (N^+-H)

Anal. Calc. for $\text{C}_{12}\text{H}_{18}\text{BrNO}_2$: C, 50.01; H, 6.29;
N, 4.86

Found: C, 50.04; H, 6.42;
N, 4.86

b) by catalytic hydrogenation

A solution of the oxime of 4,7-dimethoxy-6-methyl-1-indanone (2.0 g) in ethanol (50 ml) was hydrogenated at room temperature and pressure in the presence of platinum dioxide (0.1 g) for 12 hours (overnight). The catalyst and solvent were removed and the residue dissolved in ether, then saturated with hydrogen bromide gas to yield 1-amino-4,7-dimethoxy-6-methylindane hydrobromide (1.84 g).

4,7-Dimethoxy-1-indanone oxime

A solution of 4,7-dimethoxy-1-indanone (2.5 g) and hydroxylamine hydrochloride (2.5 g) in ethanol (15 ml) and pyridine (5 ml) was heated on a water bath for 15 minutes. The solution was then cooled and the solid which precipitated from solution was collected by filtration and washed well with cold 5% hydrochloric acid. Crystallization of the dried solid (2.1 g) from ethanol yielded the title compound, m.p. 230-232°C.

I.r. spectrum: 3210 cm^{-1} br (OH)

Anal. Calc. for $\text{C}_{11}\text{H}_{13}\text{NO}_3$: C, 63.75; H, 6.32;

N, 6.76

Found: C, 64.06; H, 6.56;

N, 6.67

Preparation of 1-amino-4,7-dimethoxyindane hydrobromide by reduction of 4,7-dimethoxy-1-indanone oxime with:a) lithium aluminum hydride

A suspension of the oxime of 4,7-dimethoxy-1-indanone (2.0 g) in sodium dried ether (100 ml) was added slowly to a stirred suspension of lithium aluminum hydride (1.5 g) in the same solvent (100 ml). The suspension was then heated under reflux for 12 hours, cooled, and the excess lithium aluminum hydride was decomposed with water. The suspension was filtered and the insoluble cake was washed well with ether. The combined ether fractions were dried over magnesium sulfate, then saturated with hydrogen

bromide gas. The solid which precipitated (0.22 g) from solution was crystallized from ethanol and ether, m.p. 225-226°C.

b) by catalytic reduction

A solution of the oxime (2.0 g) in ethanol (150 ml) was hydrogenated at room temperature and pressure in the presence of palladium-charcoal (0.1 g) for 15 hours; no hydrogen was absorbed. Acetic acid (100 ml) and palladium-charcoal (0.1 g) were then added to the above solution which was then subjected to the same hydrogenation conditions. Hydrogen was slowly absorbed over six hours. The catalyst and solvent were then removed and an oily residue remained. This residue was suspended in 5% sodium bicarbonate and extracted with chloroform. The chloroform was collected, washed well with water, saturated with hydrogen bromide gas, and evaporated. The solid which remained (0.62 g) was crystallized from ethanol and ether, m.p. 225-226°C.

The same oxime (1.2 g) in acetic acid (25 ml) and sulfuric acid (1 ml) was hydrogenated in the presence of palladium-charcoal (0.2 g). Because less than the theoretical amount of hydrogen was incorporated, an additional 0.1 g of palladium-charcoal in ethanol (50 ml) was added to the mixture and hydrogenation was continued for six hours, during which time the theoretical amount of hydrogen was absorbed. The catalyst was removed by filtration, and

the acid solution neutralized with sodium bicarbonate, then evaporated. The residue was suspended in 5% sodium bicarbonate solution, then extracted with chloroform. The chloroform extract was washed with water, dried, and saturated with hydrogen bromide gas. The solvent was evaporated, leaving a solid which was crystallized from ethanol to yield 1-amino-4,7-dimethoxyindane hydrobromide (1.1 g), m.p. 225-226°C.

I.r. spectrum: 1590, 1980, 2600-2700 cm^{-1} (N-H^+)

Anal. Calc. for $\text{C}_{11}\text{H}_{16}\text{BrNO}_2$: C, 48.19; H, 5.88;
N, 5.11

Found: C, 48.06; H, 5.79;
N, 4.82

1-Amino-6-bromo-4,7-dimethoxyindane hydrochloride

Bromine water was added dropwise to a stirred solution of 1-amino-4,7-dimethoxyindane hydrochloride (0.5 g) in water (20 ml) until a red color persisted. The solution was then stirred for two hours, basified with sodium hydroxide solution, and then extracted with ether. The ether layer was dried over magnesium sulfate, then saturated with hydrogen chloride gas. Evaporation of the solvent left an oil which crystallized from ethanol and acetone to yield a solid (0.21 g), m.p. 217-219°C. It was assumed to be the title compound.

I.r. spectrum: 1600, 2010, 2580-2680 cm^{-1} (N-H^+)

Mass spectrum: 273 (30) [$C_{11}H_{15}^{81}BrNO_2$]; 271 (30) [$C_{11}H_{14}^{79}BrNO_2$]; m/e (% rel. abund.)

Anal. Calc. for $C_{11}H_{15}BrClNO_2$: C, 42.81; H, 4.90;
N, 4.54

Found: C, 42.70; H, 4.70;
N, 4.79

6-Methoxy-1-indanone oxime

A solution of 6-methoxy-1-indanone (2.5 g) and hydroxylamine hydrochloride (2.5 g) in ethanol (30 ml) and pyridine (10 ml) was heated on a water bath for 20 minutes. The solvent was then removed, leaving a semi-solid residue which solidified when triturated with water. The solid was collected by filtration (2.5 g), then crystallized from ethanol to yield the title compound, m.p. 130-132°C.

Anal. Calc. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26;
N, 7.91

Found: C, 67.65; H, 6.30;
N, 7.90

Reduction of 6-methoxy-1-indanone oxime

A solution of the oxime of 6-methoxy-1-indanone (2.0 g) in ethanol (100 ml) and hydrochloric acid (15 ml) was hydrogenated at room temperature and pressure in the presence of palladium-charcoal (0.2 g) for 12 hours (arbitrary). The catalyst was removed by filtration and the

solvent was evaporated, leaving a solid residue. This solid (1.1 g) was suspended in acetone and filtered. The dried product melted between 240-260°C. This material proved very difficult to crystallize and melted over a wide range, 252-260°C. 1-Amino-6-methoxyindane is reported to melt at 240°C⁽²⁰³⁾.

I.r. spectrum: 1610, 2010, 2580-2600 cm^{-1} ($\text{N}^+\text{-H}$)

Anal. Calc. for $\text{C}_{10}\text{H}_{14}\text{ClNO}$: C, 60.15; H, 7.07;
N, 7.02

Found: C, 57.77; H, 6.94;
N, 11.37

1-Dimethylamino-4,7-dimethoxy-6-methylindane
hydrochloride

A solution of 1-amino-4,7-dimethoxy-6-methylindane hydrochloride (1.5 g) and 37% aqueous formaldehyde (2.0 g) in water (50 ml) was hydrogenated at room temperature and pressure in the presence of palladium-charcoal (1.5 g) for 12 hours. The catalyst was removed by filtration; the solution was then basified with ammonium hydroxide and extracted with chloroform. The chloroform layer was collected, washed with water, and then evaporated, leaving an oil. A solution of the oil in ether was then saturated with gaseous hydrogen chloride to precipitate the title compound (0.4 g) which, when crystallized from ethanol, melted at 209-211°C.

I.r. spectrum: 1600, 2300-2600 cm^{-1} (N-H^+)

Anal. Calc. for $\text{C}_{14}\text{H}_{22}\text{ClNO}_2$: C, 61.86; H, 8.16;
N, 5.15

Found: C, 62.00; H, 8.17;
N, 5.58

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